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Review

Tandem Catalysis: Synthesis of Nitrogen-Containing Heterocycles

Joana F. Campos and Sabine Berteina-Raboin *

Institut de Chimie Organique et Analytique (ICOA), Pôle de Chimie, Université d'Orléans, BP 6759, Rue de Chartres, CEDEX 2, 45067 Orleans, France; joana-filomena.mimoso-silva-de-campos@univ-orleans.fr

* Correspondence: sabine.berteina-raboin@univ-orleans.fr; Tel.: +33-238-494-856

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Abstract: In this Review, we consider all the publications since the beginning of the century that describe tandem reactions resulting in the formation of five-membered aromatic nitrogen heterocycles (thiazole, imidazole, indole, tetrazole, triazole, and isoxazole). The contents of this review are organized by taxonomy and type of tandem catalysis. It covers orthogonal, auto-, and assisted tandem catalysis, providing an overview of tandem reactions applied tonitrogen heterocycles reported in the literature up to March 2020. We believe that this compilation of data will provide a necessary starting reference to developthe applications of tandem catalysis in medicinal chemistry.

Keywords: tandem catalysis; nitrogen heterocycles; medicinal chemistry; synthesis

1. Introduction

The concept of drug-like space is widely used in modern medicinal chemistry. Key scaffold components in medicinal chemistry are the ring systems, the fundamental building blocks of most drugs on the market today. Nitrogen heterocycles (Figure 1) are among the structural components most commonly found in pharmaceuticals. Among the five-membered aromatic nitrogen heterocycles, the top five most commonly used in this class are: Thiazole, imidazole, indole, tetrazole, and benzimidazole. These five main aromatic heterocycles are found in a hundred drugs [1,2].

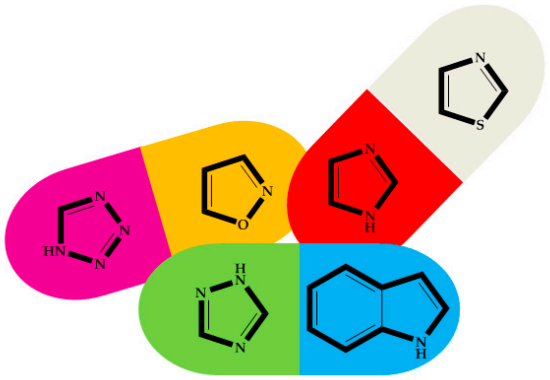


Figure 1. Five-membered aromatic nitrogen heterocycles.

Recent examples have shown that multifunctional catalytic systems can reduce the number of synthetic steps by conducting sequential catalytic processes in one synthetic operation [3,4]. Tandem catalysis is becoming increasingly important for synthesizing molecules that are relevant for medicinal chemistry. This paper is a comprehensive review of the studies reported in the literature from 2000 to March 2020 that mention tandem reactions generating five-membered aromatic nitrogen heterocycles: Thiazole, imidazole, indole, tetrazole, triazole, and isoxazole.

2. Taxonomy

In view of the numerous research advances in chemistry reported in the literature, it is important to establish a taxonomy as it allows one to represent the evolution and bring out the differences and similarities among the various methods. Especially well-documented is the recent perspective of Hayashi concerning one-pot synthesis [5]. In 2004, Fogg and dos Santos published an excellent review on tandem catalysis in which they proposed a taxonomy, distinguishing between tandem catalysis and processes that are not included in the tandem category [6].

2.1. One-Pot Synthesis of Biologically Active Molecules

One-pot reactions have always been an active research field, and in recent years, interest in catalysis research in this field has significantly increased. One of the methods that can be used to make methodologies greener is reactions in which multiple catalytic events are conducted in the same reaction flask. As pointed out by Hayashi, several terms are used to describe multi-step reactions that take place in one pot, such as: "Domino reaction", "cascade reaction" and "tandem reaction" [5].

Medicinal chemists have the ability to replicate some of the most intriguing molecules of nature in the laboratory. By applying catalytic reactions and appropriately designed synthetic processes, natural molecules and their analogs can be synthesized; the ideal strategy will always be to mimic processes that occur in nature.

2.2. Processes That Are Not Tandem Catalyses

Before discussing tandem catalysis, it is necessary to clarify the usage of other commonly encountered names such as domino or cascade reactions. Fogg and dos Santos defined one-pot catalytic processes that are not tandem catalyses [6].

3. Tandem Catalysis

Tandem catalytic transformations have been described as "coupled catalyses in which sequential formation of the substrate occurs via two (or more) mechanistically distinct processes" (see reference of Fogg and dos Santos [6]). They indicate that this catalytic reaction can be divided into three subtypes: Orthogonal, auto, and assisted, as summarized below [7,8].

3.1. Orthogonal Tandem Catalysis

Orthogonal tandem catalysis (Figure 2) uses two or more catalysts that have distinct mechanisms operating concurrently, and the substrate is transformed sequentially [6–8].

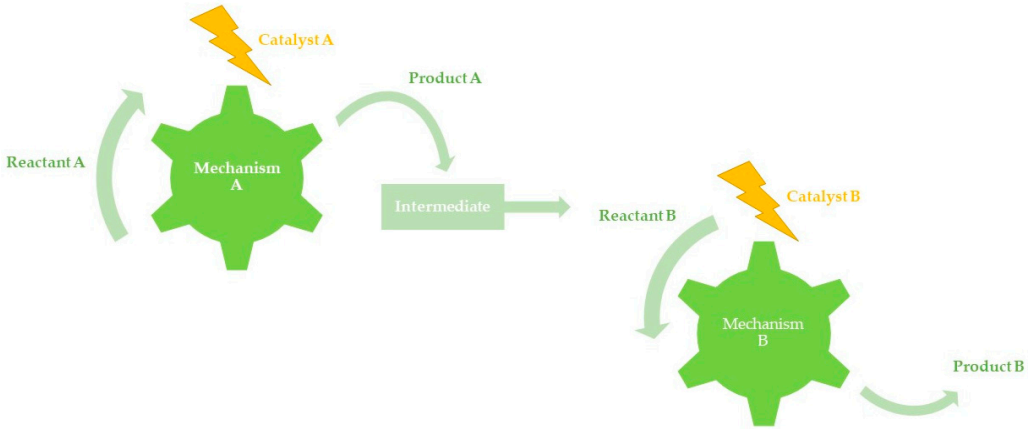


Figure 2. Schematic illustration of orthogonal tandem catalysis.

3.2. Auto-Tandem Catalysis

The so-called "auto-tandem catalysis" (Figure 3) involves several mechanistically distinct reactions that are favored by a single catalyst, the various catalytic cycles occurring spontaneously due to a cooperative interaction of all the species that are present from the beginning [6,7].

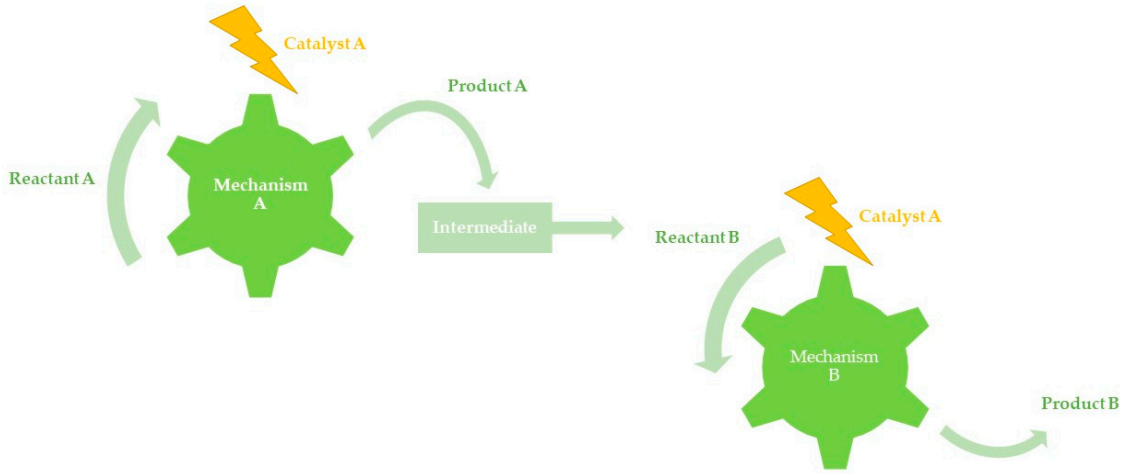


Figure 3. Schematic illustration of auto-tandem catalysis.

3.3. Assisted Tandem Catalysis

Assisted tandem catalysis (Figure 4) uses a single catalyst and requires a change in reaction conditions to bring about a shift from one catalytic mechanism to another [6,7].

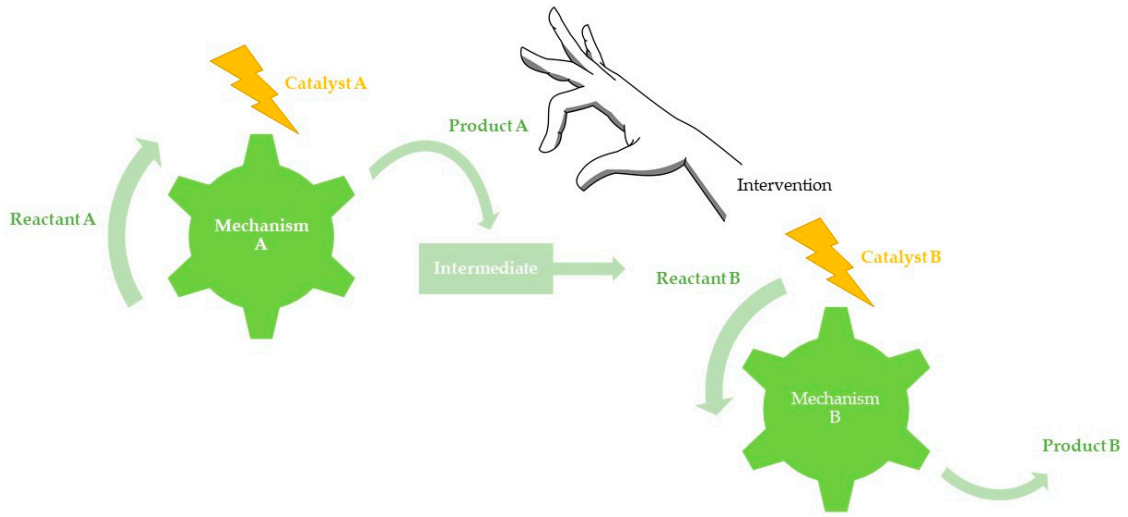


Figure 4. Schematic illustration of assisted tandem catalysis.

4. Review of Tandem Reactions Generating the Formation of Five-Membered Aromatic Nitrogen Heterocycles

4.1. Scope of Review

A comprehensive survey of the literature on tandem catalysis clearly showed that there is no systematic and comprehensive overview covering tandem reactions applied to nitrogen heterocycles [9–21]. This review, therefore, lists the uses of tandem reactions allowing the obtaining of five-membered aromatic nitrogen heterocycles since 2000.

4.2. Five-Membered Aromatic Nitrogen Heterocycles

To simplify the overview of the synthesis of five-membered aromatic nitrogen heterocycles, we have organized them into six sections: Thiazole, imidazole, indole, tetrazole, triazole, and isoxazole.

4.2.1. Thiazole

Analysis of drug structures containing a thiazole group shows a high frequency in drugs comprising the nitrogen heterocycles discussed herein and used in different pathologies (Figure 5) [2,22].

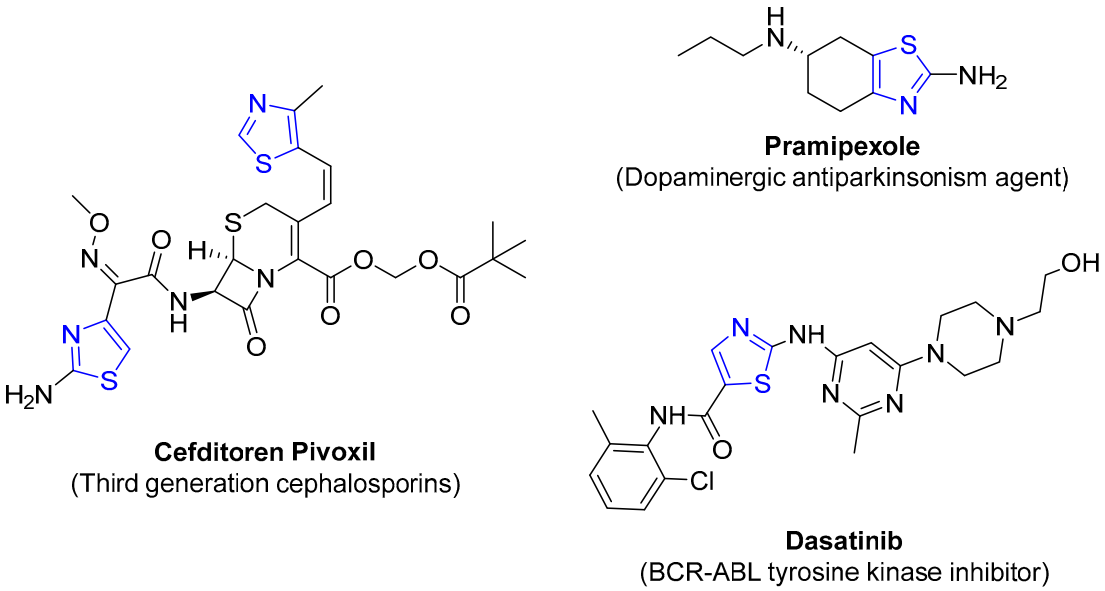
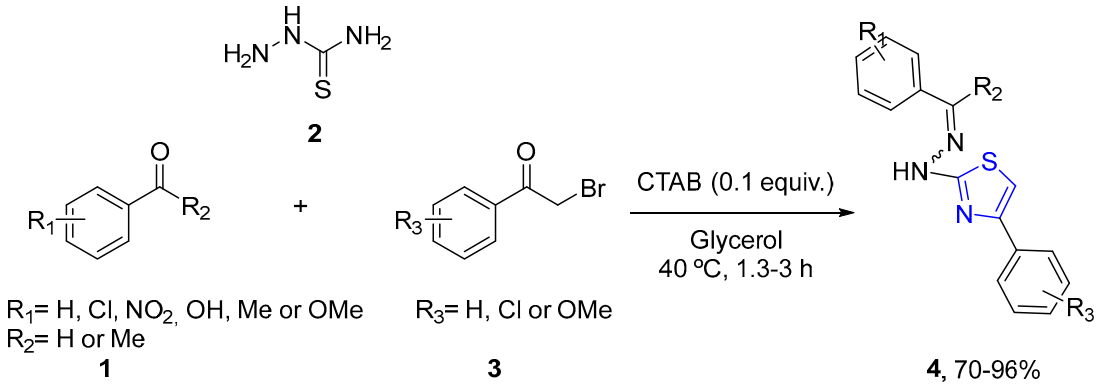


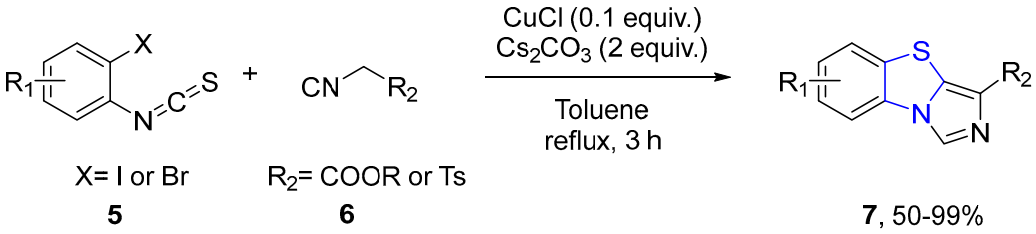
Figure 5. Drugs containing a thiazole ring.

Singh et al. described a green approach for the development of 2,4-disubstituted hydrazinyl—thiazoles **4** in glycerol micellar medium using different carbonyl compounds **1**, thiosemicarbazide **2**, and α-bromocarbonyl derivatives **3** (Scheme 1). The use of micellar catalysis in glycerol was the key aspect of this methodology that proved superior to glycerol alone. The methodology presented excellent yields, a short reaction time, and gram-scale viability [23].



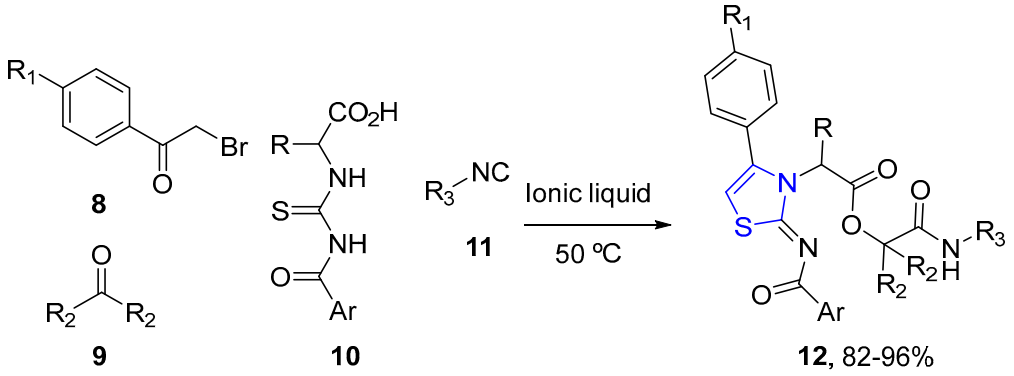
Scheme 1. Singh et al. (2018).

In 2016, Hao and co-workers described an efficient method to synthesize benzo[*d*]imidazo thiazoles **7** by the reaction of 2-haloaryl isothiocyanates **5** with isocyanides **6** (Scheme 2); this copper (I)-catalyzed tandem [3+2] cycloaddition followed by aC–S coupling reaction allowed the authors to have a simple way of developing benzo[*d*]imidazo[5,1-*b*]thiazoles in good to excellent yields [24].



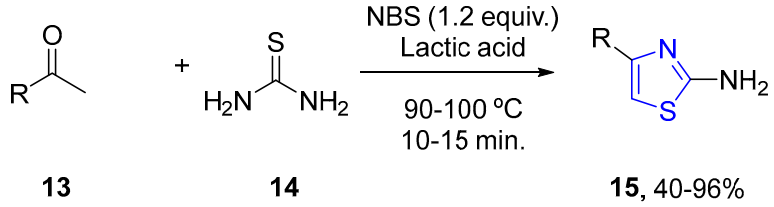
Scheme 2. Hao et al. (2016).

Shahvelayati and co-workers described a direct method for the synthesis of new α-thiazolodepsipeptide derivatives **12** via a multi-component reaction. Thiazole-containing depsipeptides were produced easily in 1-methyl-3-pentylimidazolium bromide from phenacyl bromides **8**, ketones **9**, thiourea carboxylic acid derivatives **10**, and isocyanides **11** in one step by a four-component sequence: Condensation/Passerini tandem reaction (Scheme 3) [25].



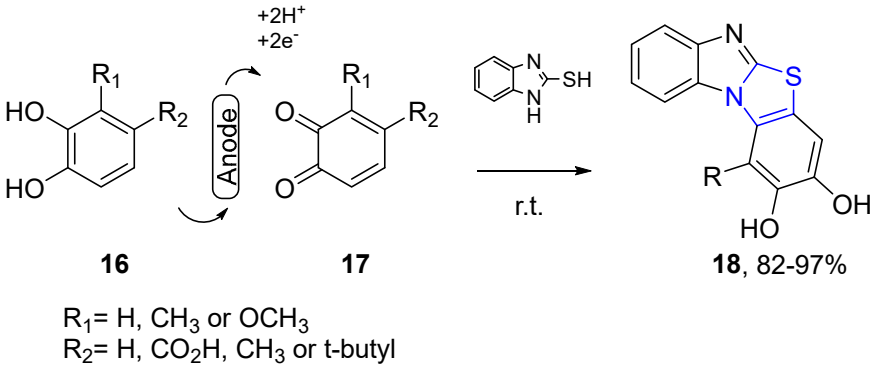
Scheme 3. Shahvelayati et al. (2016).

Bodireddy and co-workers, in 2016, generated Hantzsch 2-aminothiazole derivatives **15** in good yields within 10–15 min from aralkyl ketones **13** through in situ regioselective α-bromination followed by heterocyclization in the presence of thiourea **14** in lactic acid at 90–100 °C. This sequence in a single step (Scheme 4) using lactic acid as solvent and catalyst allowed the tandem one-pot synthesis of Hantzsch 2-aminothiazole derivatives **15** [26].



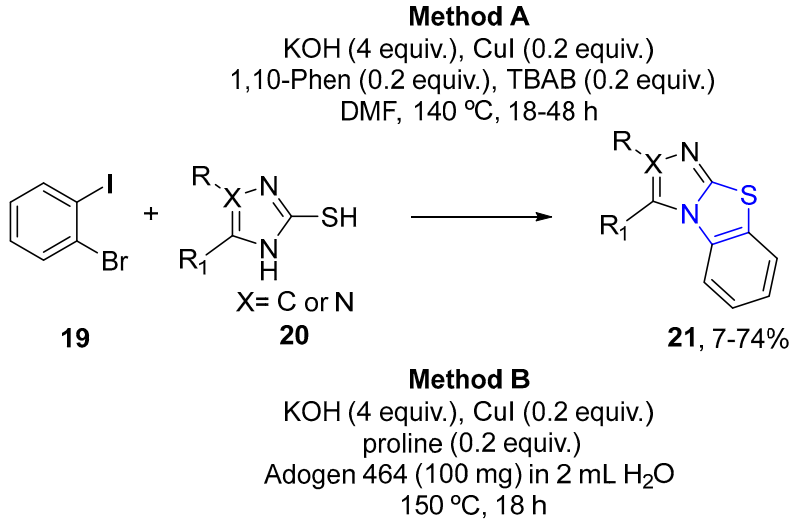
Scheme 4. Bodireddy et al. (2016).

Khodaei et al. obtained tetracyclic imidazo[2,1-*b*]thiazoles **18** via electrochemically induced tandem heteroannulation reactions. The catechol-fused tetracyclic compounds were synthesized in aqueous solution through the anodic oxidation of catechols in the presence of 2-mercaptobenzimidazole. The benzimidazo[2,1-*b*]thiazoles **18** were obtained through a domino reaction of commercially available starting materials **16**–**17** [27]. Besides the high efficiency and atom economy as a domino process, this reaction where only electrons are used as reagents is an environmentally benign transformation compared to oxidative ones (Scheme 5).



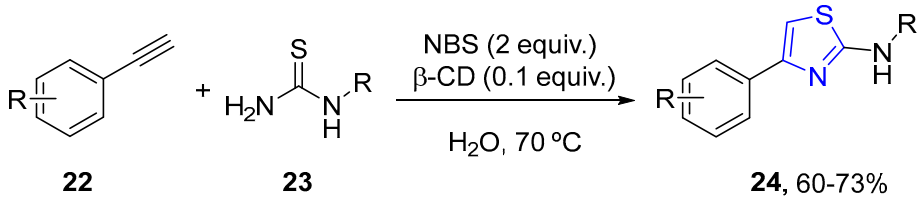
Scheme 5. Khodaei et al. (2013).

The Beresneva group developed a simple method for the preparation of benzofusedimidazo[2,1-*b*]thiazoles and [1,2,4]triazolo[5,1-*b*][1,3]benzothiazole **21** in the system solid KOH/CuI/1,10-phen/TBAB/DMF from 1-bromo-2-iodobenzene **19** and corresponding thiols **20** by S,N-tandem arylation reactions (Scheme 6) [28].



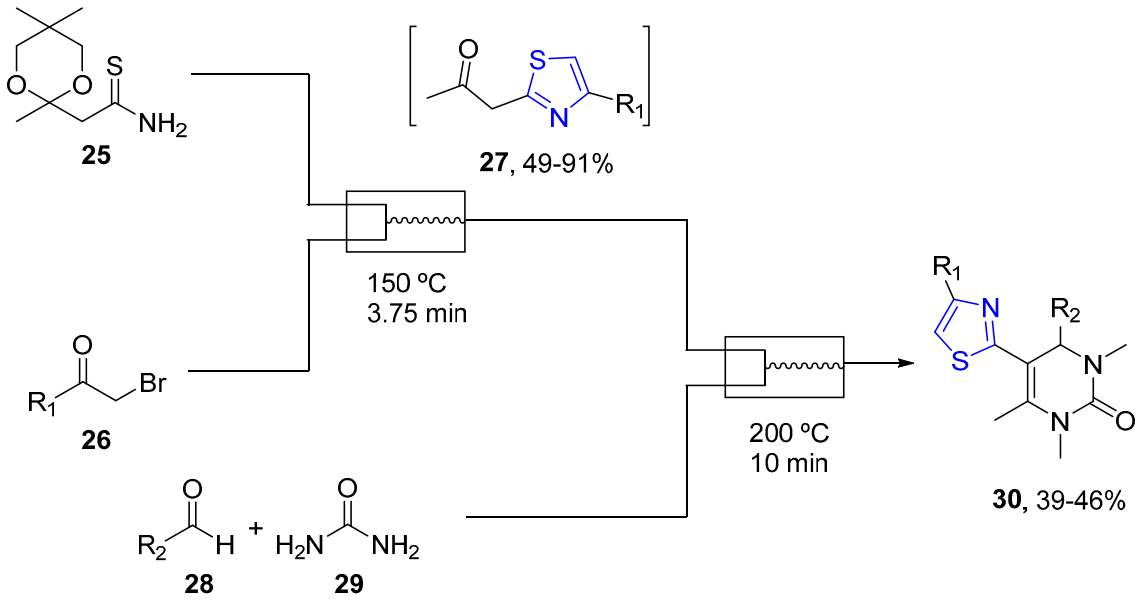
Scheme 6. Beresneva et al. (2013).

Madhav and co-workers reported, for the first time, the use of the one-pot tandem procedure for the synthesis of thiazoles/selenazoles from alkynes **22**, forming 2,2-dibromo-1-phenylethanone as an intermediate. The group developed a convenient one-pot aqueous phase synthesis of substituted thiazoles **24** under mild conditions in good yields (Scheme 7) [29].



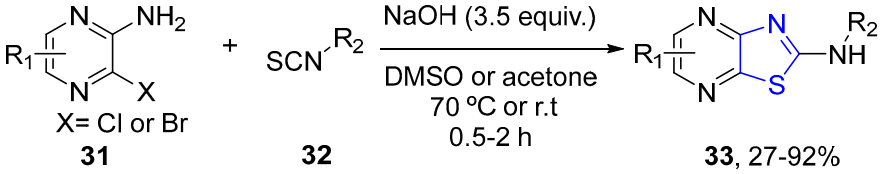
Scheme 7. Madhav et al. (2012).

Pagano et al. developed a tandem approach via the multistep continuous flow assembly of 2-(1*H*-indol-3-yl)thiazoles using a Syrris AFRICA® synthesis station (Scheme 8). In this work, the team imagined the formation of heterocycles byconsecutive reactions using anautomated continuous flow process. This one allowed them to access a novel class of indolylthiazoles **30** [30].



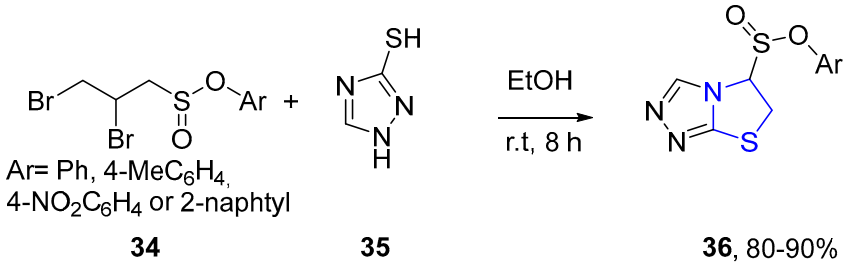
Scheme 8. Pagano et al. (2012).

In 2012, the Kwak group reported the synthesis of N-substituted-2-aminothiazolo[4,5-*b*] pyrazine **33** by tandem reaction of *o*-aminohalopyrazines **31** with isothiocyanates **32** (Scheme 9) [31].



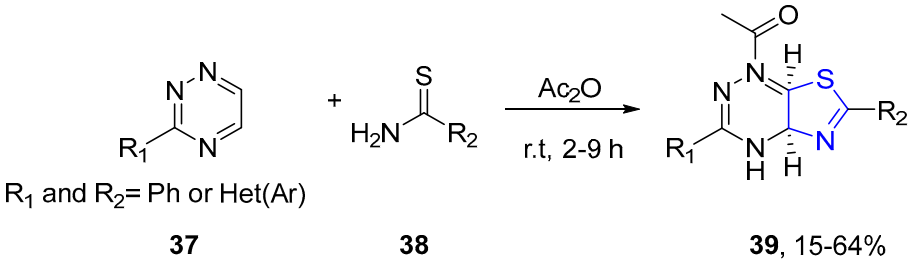
Scheme 9. Kwak et al. (2012).

In 2005, Shklyarenko et al. reported a convenient procedure by S,N-tandem alkylation of 1,2,4-triazole-3-thiol **35** with vicinal dibromopropyl sulfones **34** for the synthesis of triazolothiazolidines **36** in ethanol at room temperature for 8 h (Scheme 10) [32].



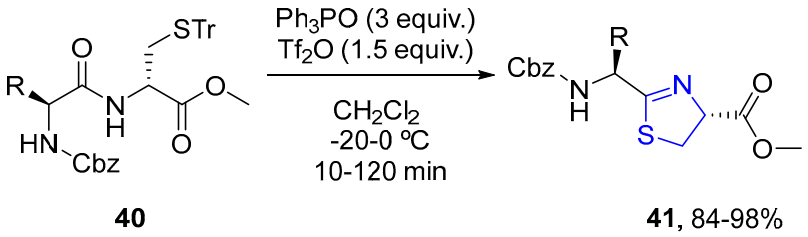
Scheme 10. Shklyarenko et al. (2005).

Tandem nucleophilic addition (A_N—A_N) of bifunctional reagents to azines, tandem substitutions (S_N^H—S_N^H), and their various combinations (A_N—S_N^{ipso}) have found increasing use as convenient procedures for the synthesis of fused heterocyclic systems. Mochulskaya et al. demonstrated the tandem A_N—A_N reactions of 3-aryl-1,2,4-triazines **37** with aromatic thioamides and thiosemicarbazides in acetic anhydride at room temperature. This provided a convenient approach to the synthesis of thiazolo[4,5-*e*]annelated tetrahydrotriazines, which underwent aromatization under the action of potassium permanganate to give thiazolo[4,5-*e*][1,2,4]triazines, thus completing the tandem S_N^H—S_N^H reactions (Scheme 11) [33].



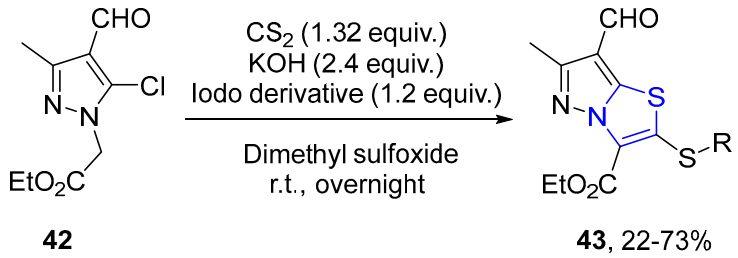
Scheme 11. Mochulskaya et al. (2004).

You and co-workers described an efficient biomimetic synthesis of thiazolines by treating N-acylated cysteine substrates **40** with hexaphenyloxodiphosphonium tri-fluoromethanesulfonate to activate the amide group. The reaction proceeded in high yield with a retention of configuration at the C4-and C2-exomethine carbon atoms of the thiazoline **41**. The application of this method to tandem dehydrocyclizations afforded a thiazole-thiazoline product with excellent stereocontrol and in good overall yield (Scheme 12) [34].



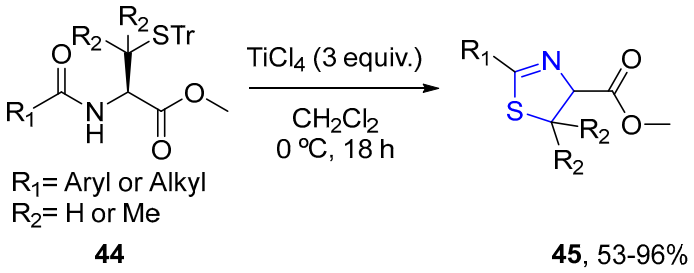
Scheme 12. You et al. (2003).

In 2000, Wang et al. synthesized pyrazolo[5,1-*b*]thiazole **43** by a tandem reaction, in whichethyl1-pyrazolacetatereacted with carbon disulfide and an iodo derivative. From **42**, prepared previously by the Vilsmeier–Haack reaction and using a tandem reaction, compounds **43** were synthesized. For the preparation of **43,** compound **42**, carbon disulfide, and potassium hydroxide were stirred overnight, and the iodo derivative was then added to give the ring-closed expected compound (Scheme 13) [35].



Scheme 13. Wang et al. (2000).

The Raman group studied the possible extent of $TiCl_4$-mediated $_{\Delta}{}^2$-thiazoline synthesis by deprotection−dehydrocyclization of trityl-protected cysteine N-amides **44** in a tandem procedure (Scheme 14) [36]. The $TiCl_4$-mediated tandem deprotection-cyclodehydration of simple trityl-protected cysteine N-amide derivatives proved to be a versatile process for the synthesis of thiazolines **45** with generally good stereoselectivities.



Scheme 14. Raman et al. (2000).

Final note on Thiazole: The synthesis methodologies reported by the different teams demonstrated a preference for the use of Cu as a catalyst system for thiazole derivative synthesis reactions.

4.2.2. Imidazole

The second most common five-membered aromatic nitrogen heterocycle is imidazole. Imidazole is an important biological interesting heterocycle that is present in the amino acid histidine and possesses catalyst and acid–base functionalities. Imidazole-containing drugs were subdivided into two classes: Monocyclic imidazoles and benzimidazoles; in this review we focus on monocyclic imidazoles (Figure 6) [2,22].

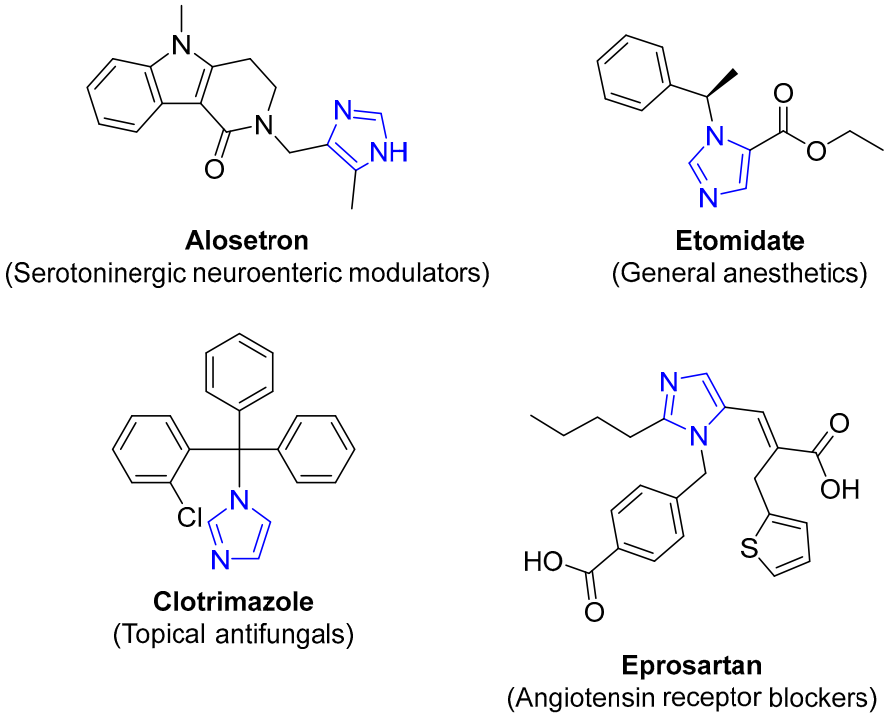
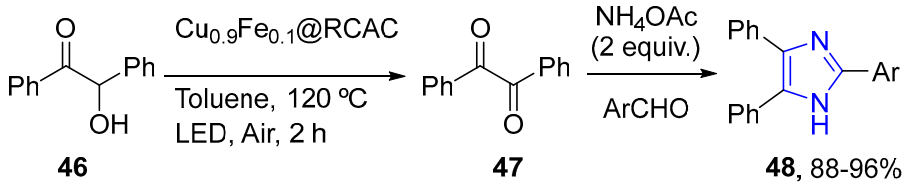


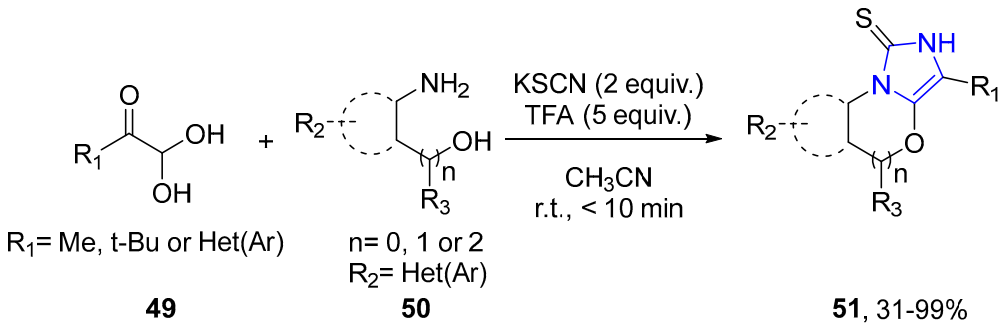
Figure 6. Drugs containing an imidazole ring.

Banerjee et al. reported a tandem one-pot process for the sequential oxidation of alcohol **46** followed by condensation to functionalized imidazole **48** in excellent yields using Cu0.9Fe0.1@RCAC as a catalyst (Scheme 15). The study validated the visible light-emitting diode light-driven selective and efficient aerobic oxidation of primary/secondary alcohols to aldehydes/ketones and oxidative azo-coupling of anilines [37].



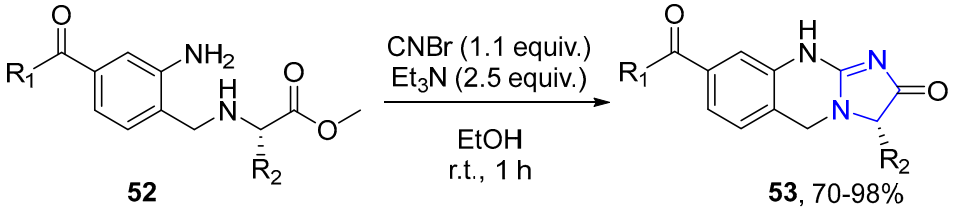
Scheme 15. Banerjee et al. (2019).

Yu et al. achieved the synthesis of [1,3]oxazine N-fused imidazole-2-thiones **51** from glyoxal monohydrates **49,** amino alcohols **50**, and KSCN (Potassium thiocyanate) (Scheme 16). This strategy resulting from a tandem reaction underwent imine formation/intramolecular cyclization/[3+2] cycloaddition. The final products demonstrated a wide variation in functional groups and additionally high efficiency on the gram-large scale [38].



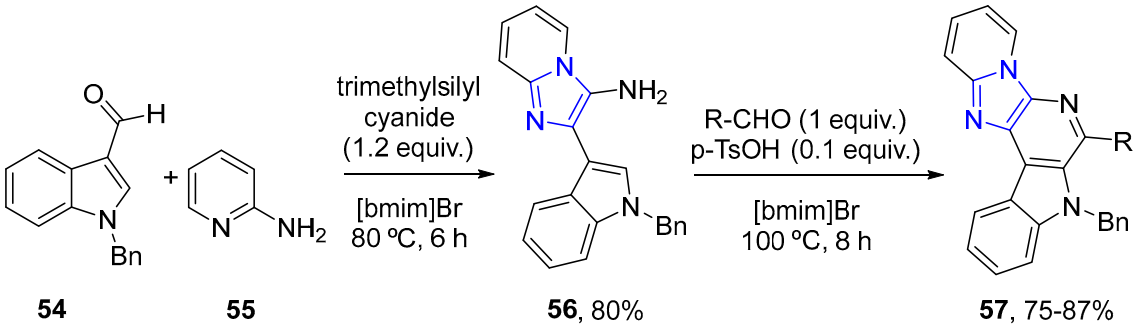
Scheme 16. Yu et al. (2018).

Kumar et al. reported a protocol for the enantiospecific synthesis of novel (S)-3-substituted imidazo[2,l-*b*]quinazoline-2-ones **53** via the tandem reaction of substituted (S)-3-amino-4-aminomethyl benzoates **52** and cyanogen bromide under basic conditions. This process involved the addition reaction of substituted (S)-3-amino-4-aminomethylbenzoatesto CNBr to yield 2-iminotetrahydroquinazoline carboxylate intermediates. After an in situ intramolecular aminolysis, the triheterocyclicimidazo[2,l-*b*]quinazoline-2-ones **53** were obtained in good yields (Scheme 17) [39].



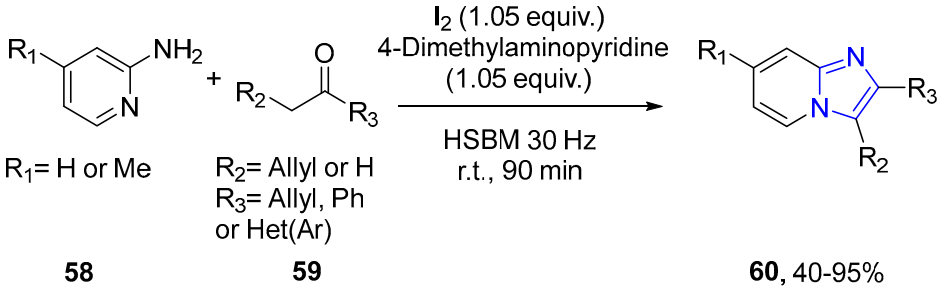
Scheme 17. Kumar et al. (2017).

Yan and co-workers carried out a very efficient tandem process for the synthesis of pyridoimidazo-fused ß-carbolines **57**. These compounds were obtained by a one-pot three-component reaction of 1-benzyl-1*H*-indole-3-carbaldehyde **54**, 2-aminopyridine **55**, and trimethylsilyl cyanide via the Groebke–Blackburn–Bienaymé reaction; then, acyclization through the Pictet–Spengler reaction of the resulting imidazo[1,2-*a*]pyridine **56** allowed access to the desiredheterocycles **57** (Scheme 18) [40].



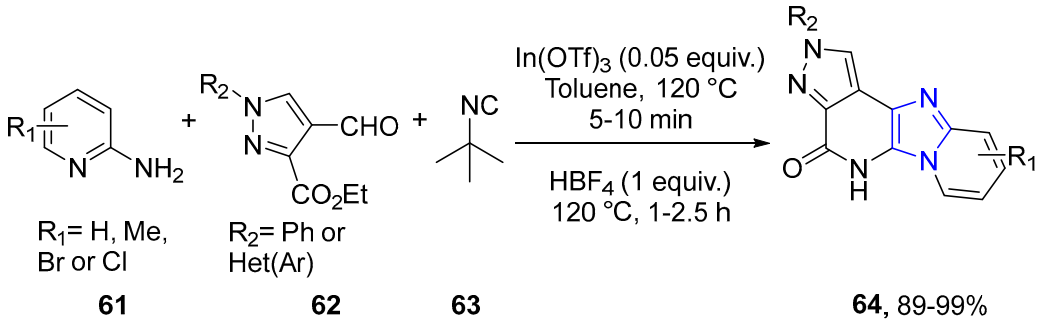
Scheme 18. Yan et al. (2017).

Wang et al. investigated an I_2/DMAP-promoted amination/cyclization of methyl ketones or 1,3-dicarbonylcompounds with 2-aminopyridines **59**. This team showed that a wide range of acetophenones were suitable substrates for this tandem cyclization reaction, including both electron-rich and electron-deficient groups on the para-, meta-, or ortho-position of the aryl ring.Theexpected2-aryl-imidazo[1,2-*a*]pyridines **60** were synthesized in good yields (Scheme 19) [41].



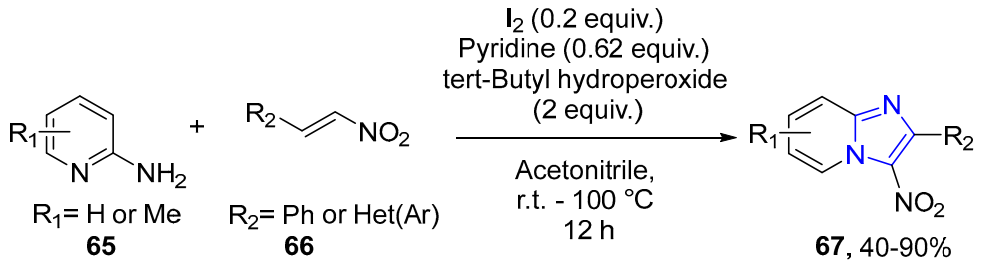
Scheme 19. Wang et al. (2016).

Devi et al. managed to obtain pyrazolopyridinone-fused imidazopyridines **64** from 4-formyl-1*H*-pyrazole-3-carboxylates **62**, 2-aminopyridines **61**, and tert-butyl isonitrile as the starting materials in moderate to good yields. The results were achieved using $In(OTf)_3$-HBF_4 as an efficient catalytic system (Scheme 20) [42].



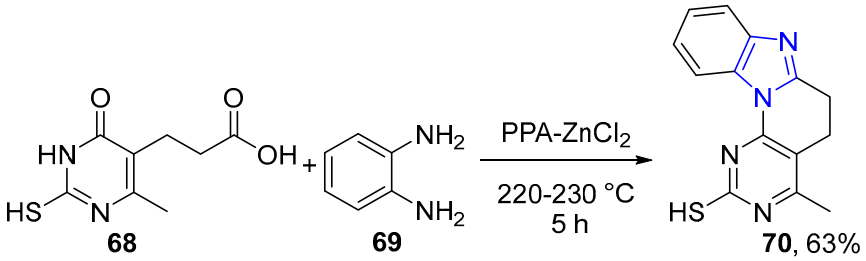
Scheme 20. Devi et al. (2016).

The group of An, through a tandem reaction of Michael addition and oxidative coupling, developed a metal-free approach to the obtaining of imidazo[1,2-*a*]pyridine **67** using iodine–t-butyl hydroperoxide–pyridine as a catalyst. The catalytic system was obtained sequentially (Scheme 21) [43].



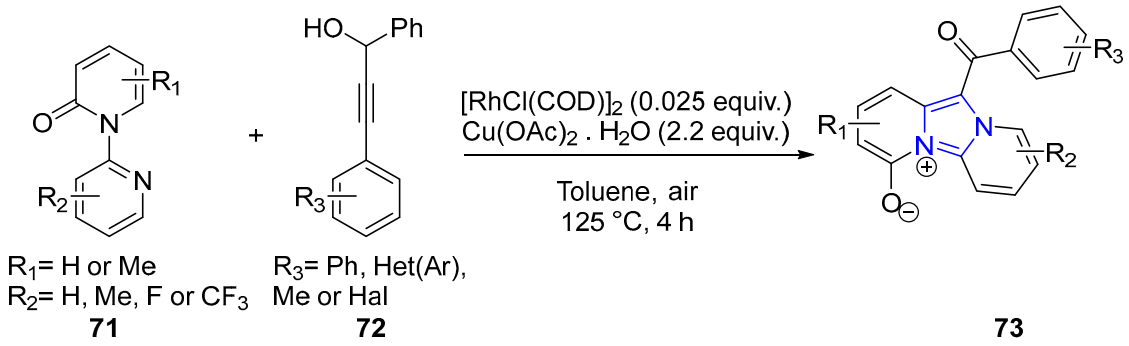
Scheme 21. An et al. (2016).

In 2015, Harutyunyan monitored the reaction of substituted 2-mercaptopyrimidin-5-yl propanoic acid **68** with 1,2-benzenediamine **69** in polyphosphoric acid (PPA) with the presence of $ZnCl_2$ (Scheme 22) [44].



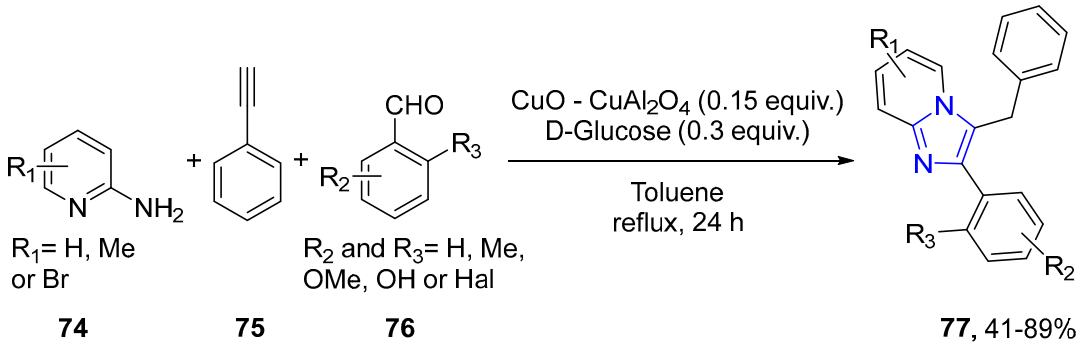
Scheme 22. Harutyunyan (2016).

The group of Li reported the rhodium catalysis synthesis of 11-acylated imidazo[1,2-*a*:3,4-*a*′] dipyridin-5-ium-4-olates **73**. These results were achieved using rhodium-catalyzed/copper-mediated tandem C(sp2)−H alkynylation followed by intramolecular annulation of 2*H*-[1,2′-bipyridin]-2-ones **71** with various propargyl alcohols **72** (Scheme 23) [45].



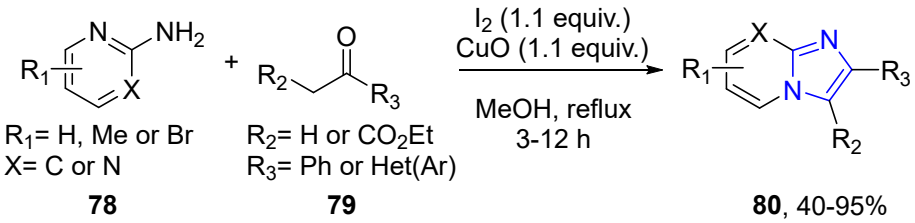
Scheme 23. Li et al. (2016).

Balijapalli and Iyer, by adopting a one-pot tandem process using D-glucose and a copper(II) oxide-copper(II) aluminate composite, were able to synthesize imidazo[1,2-a]pyridines **77** from 2-aminopyridines **74**, phenylacetylene, and aromatic aldehydes **76** (Scheme 24) [46]. For that, the D-glucose and the copper(II)oxide/copper aluminate composite (5 wt.% CuO-$CuAl_2O_4$)-catalyzed conditions were previously optimized.



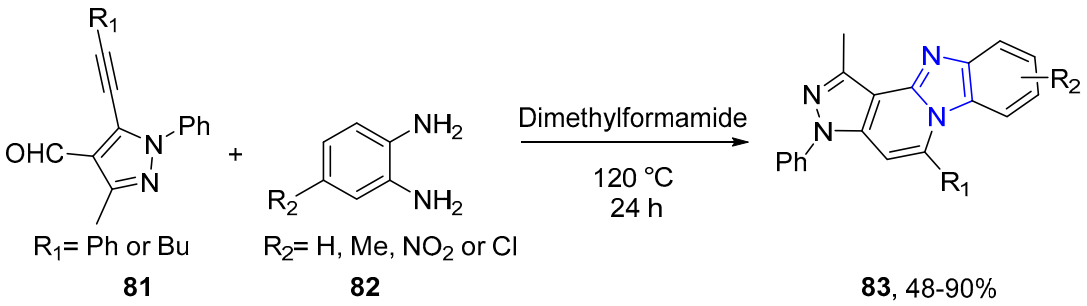
Scheme 24. Balijapalli and Iyer (2015).

The Cai group successfully employed an I_2/CuO-promoted tandem strategy for the synthesis of zolimidine pharmaceutical drug derivatives. The I_2/CuO-promoted one-pot protocol was developed to generate 2-substituted imidazo[1,2-a]pyridines **80** via 2-aminopyridines **78** reacting on α-iodo acetophenones generated in situ from aryl methyl ketones **79** in MeOH in good yields (Scheme 25) [47].



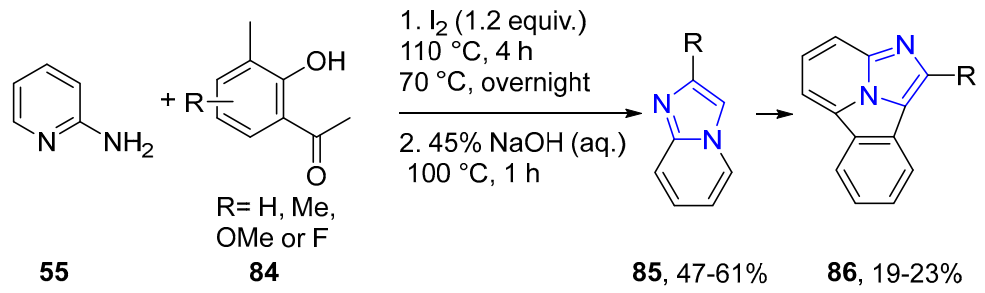
Scheme 25. Cai et al. (2015).

The Milišiūnaitė group performed tandem cyclization for the synthesis of pyrazolo[4,3:3,4] pyrido[1,2-*a*]benzimidazoles **83**. By heating 3-alkynyl- or 5-alkynyl pyrazole-4-carbaldehydes **81** and benzene-1,2-diamines **82** in DMF, the team was able to synthesize several derivatives using copper-free tandem cyclization (Scheme 26) [48].



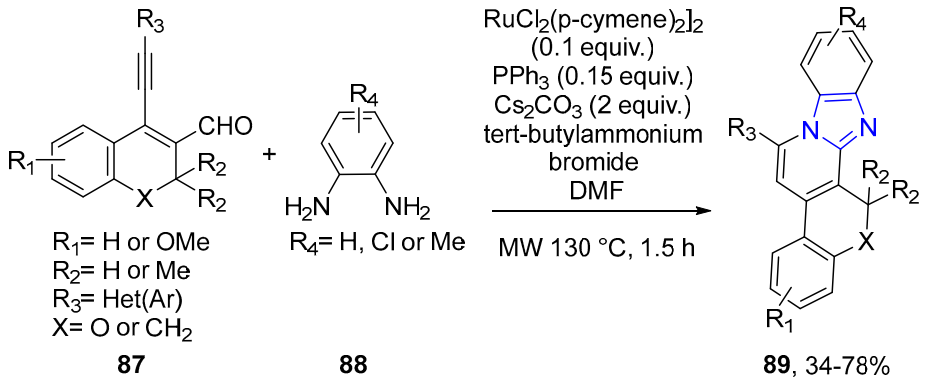
Scheme 26. Milišiūnaitė et al. (2015).

Stasyuk and co-workers employed a tandem [8+2] cycloaddition [2+6+2] dehydrogenation protocol for the preparation of benzo[*a*]imidazo[5,1,2-*cd*]indolizines **86**. The synthesis of several derivatives capable of undergoing the ESIPT (excited state intramolecular proton transfer) process was achieved from 2-(20-hydroxy-phenyl)-imidazo[1,2-*a*]pyridines **85**. Compounds **85** were prepared from acetophenones **84** and 2-aminopyridine via an Ortoleva–King reaction followed by Chichibabin ring closure. Then, **85** were subsequently reacted with a benzyne precursor in the presence of cesium fluoride and an 18-crown-6 ether (Scheme 27) [49]. This work comes from the continuation of the study of these procedures by this team [50].



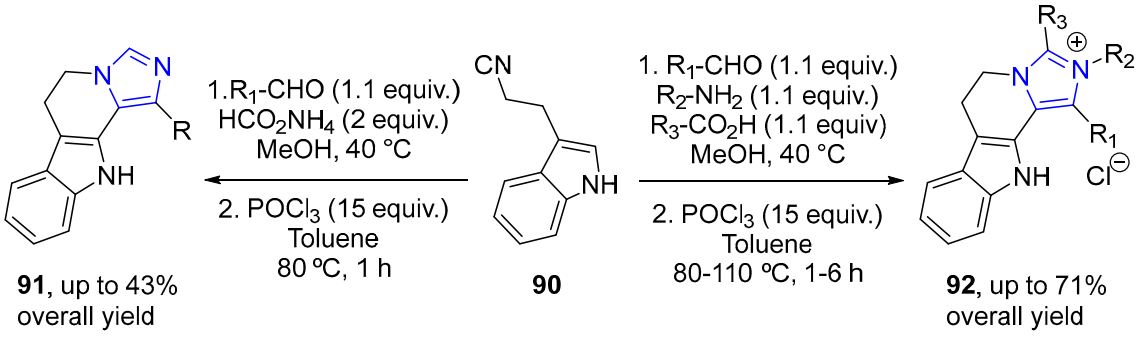
Scheme 27. Stasyuk et al. (2014).

Manna and Panda published the synthesis of benzimidazoles **89** through a metal-catalyzed endo-cyclization approach involving imine and alkyne activation. The team developed a microwave-assisted protocol to synthesize benzimidazole-fused derivatives with high regioselectivity. This procedure involved the nucleophilic addition of ortho-alkynyl aldehydes **87** and benzenediamines **88** using $[RuCl_2(p\text{-cymene})_2]_2$-catalyzed tandem cyclization followed by the formation of three new N–C bonds and two heterocyclic rings. This process in one pot gave fused polycyclic heterocycles (Scheme 28) [51].



Scheme 28. Manna and Panda (2014).

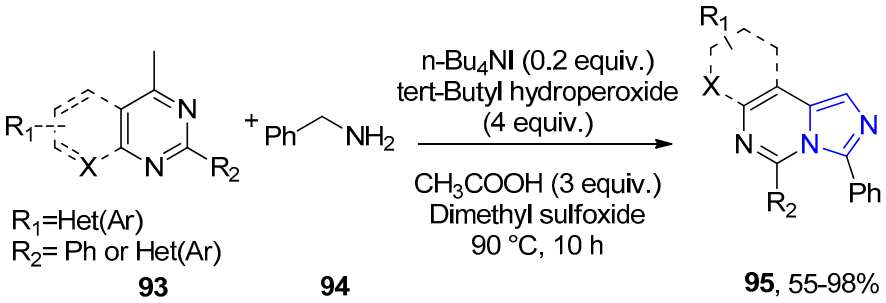
Silvani and co-workers prepared 6,11-dihydro-5*H*-imidazo[1′,5′:1,2]pyrido[3,4-*b*]indol-2-ium salt and indole **91**–**92** derivativesthrough a sequential Ugi reaction followed by a Bischler–Napieralski/ heterocyclization tandem closure (Scheme 29) [52]. This protocol was achieved successfully from readily available starting materials and can be applied to the elaboration of a wide range of heterocyclic compounds. These structuresalso carriedup to three points of interesting chemical diversity.



Scheme 29. Silvani et al. (2014).

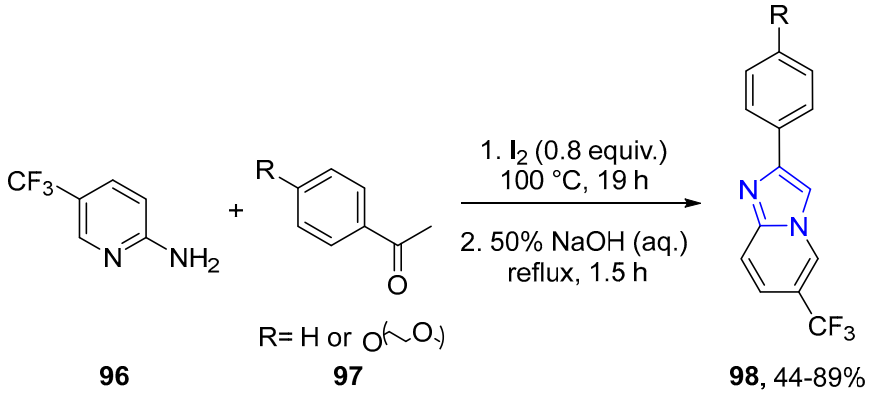
The Zhao group efficiently catalyzed a domino reaction that involved the selective dual amination of sp3 C–H bonds using n-Bu_4NI as a catalyst (Scheme 30) [53]. The imidazo[1,5-*c*]quinazolines **95** were

prepared via a tandem reaction following sp3 C–H functionalization under metal-free conditions and they also reported the rare method of benzylic primary C–H oxidative amination with primary amines.



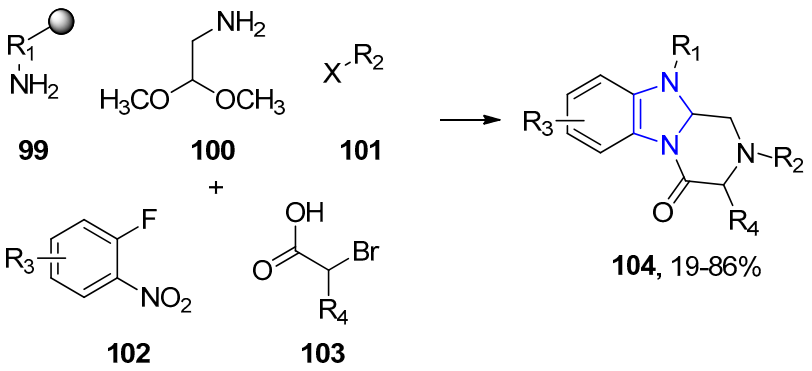
Scheme 30. Zhao et al. (2014).

The Ciuciu group adopted the Ortoleva–King–Chichibabin tandem process for the preparation of complex imidazo[1,2-a]pyridine **98**. A short and efficient route to obtain imidazo[1,2-*a*]pyridine from 2-amino-5-(trifluoromethyl)pyridine **96** and acetophenones **97** was achieved (Scheme 31) [54].



Scheme 31. Ciuciu et al. (2014).

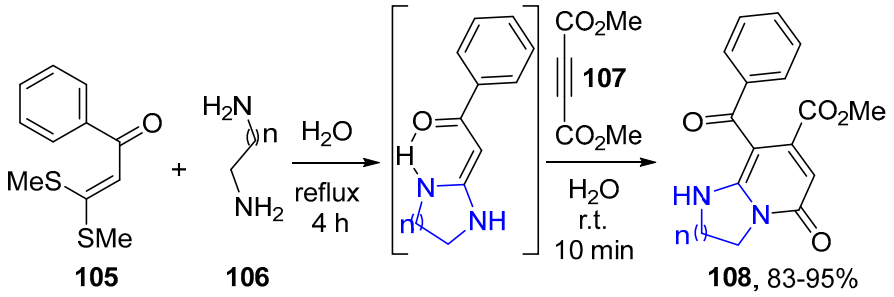
Ventosa-Andrés et al. reported the synthesis of benzimidazolinopiperazinones **104** via a tandem N-acyl-N-aryliminium ion cyclization–nucleophilic addition reaction using commercially available building blocks **99**–**103** (Scheme 32) [55]. This work is the logical continuation of the study of these procedures by this team [56].



Scheme 32. Ventosa-Andrés et al. (2014).

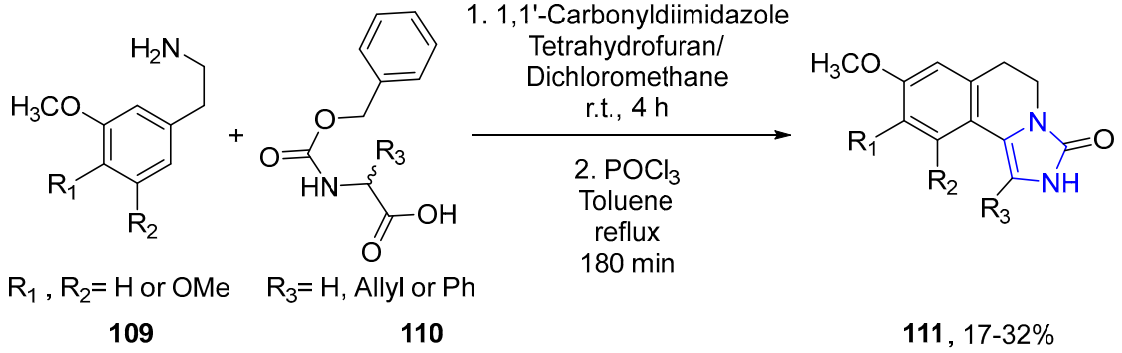
The group of Chanu reported the synthesis of tetrahydroimidazopyridines **108** under water in a one-pot procedure and using three-component **105**–**107** tandem annulation from α-oxoketene S,S–acetals (Scheme 33) [57]. The authors concluded that heterocyclic ketene aminals with an enamine

moiety (HN–C=C) were found to act as ambident nucleophiles. Due to the conjugation effect of the electron-donating amino groups and the electron-withdrawing substituents, the double bond was highly polarized, which made it particularly convenient to usein the Michael addition reactions with DMAD (dimethyl acetylenedicarboxylate). Moreover, it should be noted that among the benzoylketene N,N-acetals, ortho-halo group substituted ones broaden the scope of this reaction to diversity-oriented synthesis by further intramolecular tandem annulations.



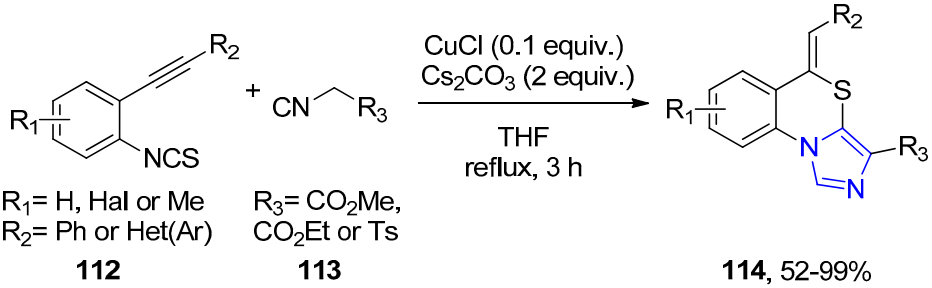
Scheme 33. Chanu et al. (2014).

Cherney and co-workers performed the tandem cyclization reactions of electron-rich arylethylamino acid amides (Scheme 34) [58]. A straightforward route to the dihydroimidazo-isoquinolin-3(2H)-one **111** ring system was achieved using a tandem cyclization strategy under Bishler–Napieralski conditions. This approach, in enabling the preparation of a 3,4-dihydroisoquinoline ring system through an intramolecular dehydration reaction of an arylethylamide **109**,was typically accomplished under strongly acidic conditions.



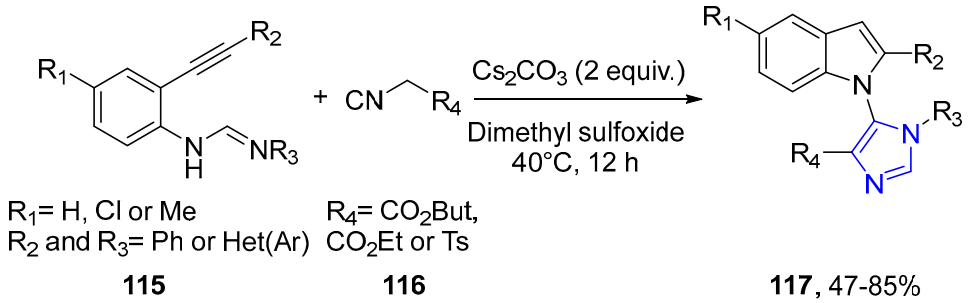
Scheme 34. Cherney et al. (2014).

The group of Hao succeeded in the rapid synthesis of 5*H*-benzo[*d*]imidazo-[5,1-*b*][1,3]thiazines **114** by a copper(I)-catalyzed tandem reaction of *o*-alkynylphenyl isothiocyanates **112** with isocyanides **113** in THF with Cs_2CO_3 as a base in good yields (Scheme 35) [59].



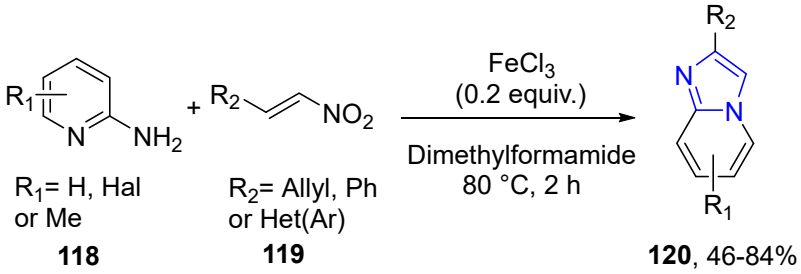
Scheme 35. Hao et al. (2014).

In 2014, again, the same group of Hao reported a route to build indolyl imidazole derivatives **117** using a tandem approach. The reaction was performed under mild conditions with high efficiency (Scheme 36) [60]. In the reaction, a [3+2] cycloaddition of isocyanide to carbodiimide and intramolecular cyclization were involved.



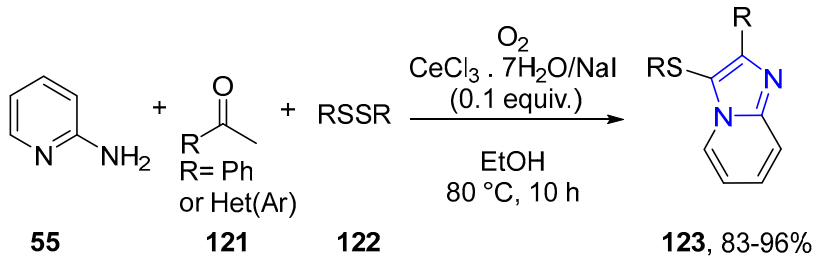
Scheme 36. Hao et al. (2014).

Santra et al. investigated the synthesis of imidazo[1,2-*a*]pyridines **120** using Iron(III) as a catalyst and showed a new route to obtain Zolimidine, a useful drug implied for the treatment of peptic ulcer. This reaction was achieved in two steps. The first step of the reaction was the Michael addition of 2-aminopyridine **118** with nitroolefin **119**; the second step was intramolecular cyclization, leading to the final product **120** after removal of water and nitroxyl (Scheme 37) [61].



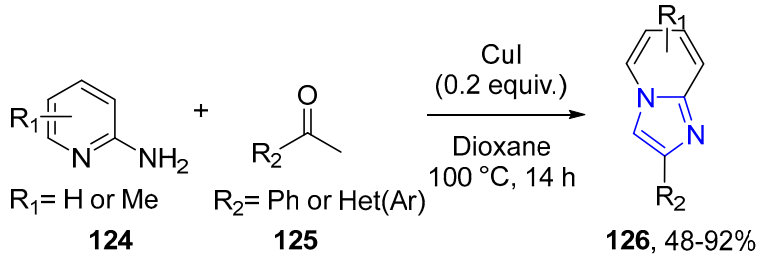
Scheme 37. Santra et al. (2013).

Ge and co-workers achieved an aerobic multicomponent tandem synthesis of sulfenylimidazo[1,2-*a*]pyridines **123** (Scheme 38) [62]. This one-pot reaction protocol involved the formation of imidazo[1,2-*a*]pyridines followed by Friedel–Crafts sulfenylation under mild conditions. From 2-aminopyridine **55**, ketones **121**, disulfides **122**, and $CeCl_3 \cdot 7H_2O$/NaI as catalysts, the team was able to develop the synthesis of 3-sulfenylimidazopyridines **123**.



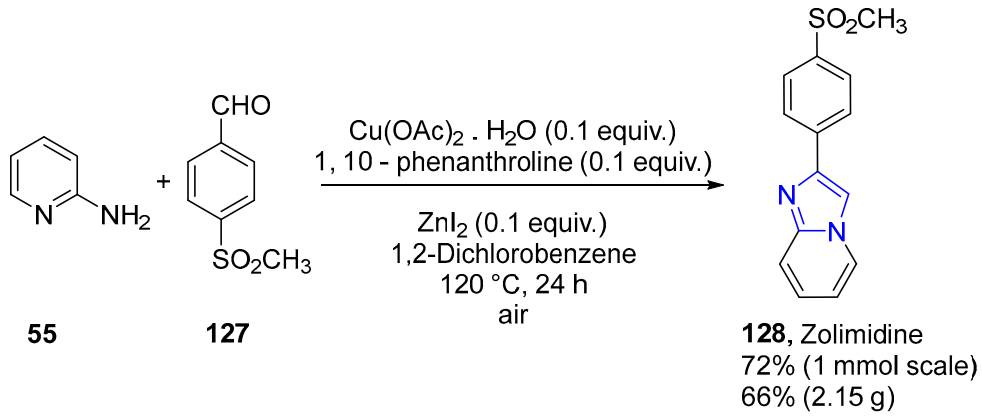
Scheme 38. Ge et al. (2013).

The Pericherla team reported a copper-catalyzed tandem process to achieve imidazo[1,2-*a*] pyridines **126**. The strategy privileged was the copper-catalyzed tandem imine formation and intramolecular aerobic oxidative C–H bond amination/cyclizations. The various derivatives were prepared from 2-aminopyridines **124** and acetophenones **125** in good yields (Scheme 39) [63].



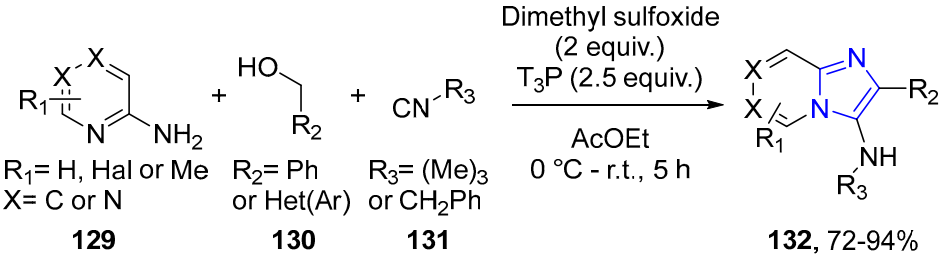
Scheme 39. Pericherla et al. (2013).

Bagdi et al. demonstrated that the same system could be used under ambient air. Some functionalized imidazo[1,2-*a*]pyridines were synthesized, and the protocol developed also successfully provided the direct preparation of zolimidine (**128**) on a large scale (Scheme 40) [64].



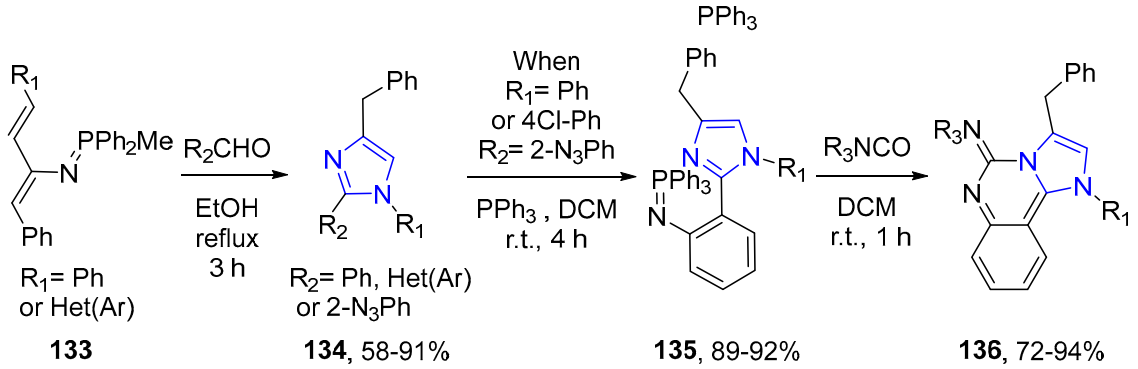
Scheme 40. Bagdi et al. (2013).

Ramesha and co-workers published a tandem approach for the synthesis from a variety of alcohols **130**. Alcohols were oxidized in situ to aldehydes, which, in turn, underwent a three-component reaction with various 2-amino derivatives **129** and isocyanides **131** to afford imidazo[1,2-*a*]pyridines **132** in excellent yields (Scheme 41) [65].



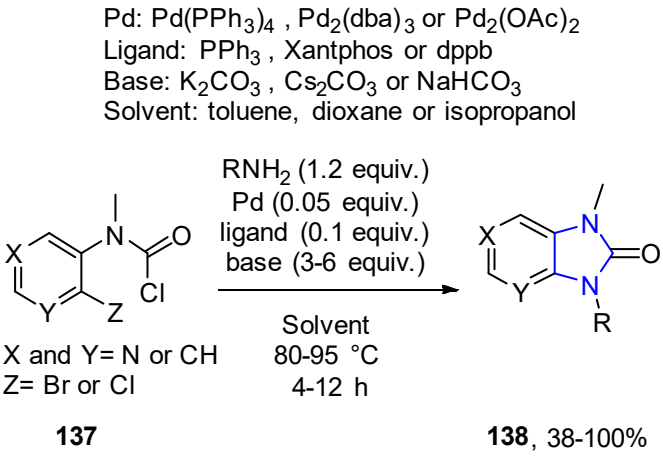
Scheme 41. Ramesha et al. (2013).

The team of Nie worked on the preparation of 1,2,4-trisubstituted imidazoles and imidazo[1,2-c] quinazolines. These reactions were conducted with a tandem aza-Wittig/electrocyclic ring-closure process (Scheme 42) [66]. The library of 1,2,4-trisubstituted imidazoles **136** was synthesized efficiently from vinyliminophosphoranes **133** and aldehydes. A tandem aza-Wittig reaction of iminophosphorane **135** with isocyanate generated imidazo[1,2-c]quinazolines **136** in high yields.



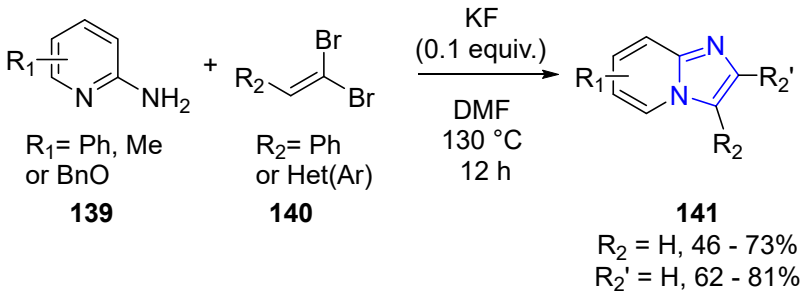
Scheme 42. Nie et al. (2012).

Lach and Koza successfully developed a cascade ureidation/palladium-catalyzed cyclization to access the imidazo[4,5-*b*] and [4,5-*c*]pyridine-2-ones **138** series from carbamoyl chlorides **137** (Scheme 43) [67].



Scheme 43. Lach and Koza (2012).

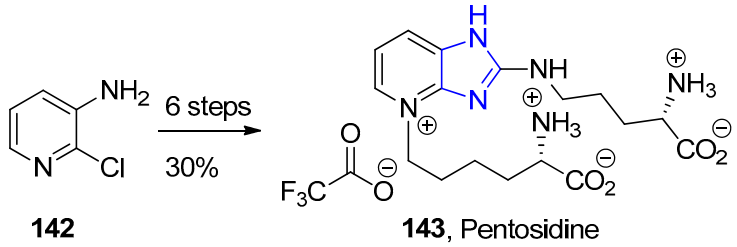
Liu and co-workers reported the synthesis of 2- and 3-substituted imidazo[1,2-*a*]pyridines **141** from 2-aminopyridine **139** derivatives and gem-dibromovinyl compounds **140** by the tandem nucleophilic substitution (or nucleophilic addition)/cyclization reaction. The team assumed that the reaction probably involved 1-bromoalkyne generated in situ from the dehydrohalogenation of gem-dibromovinyl substrates. They suggested that subsequently, the nucleophilic substitution and nucleophilic addition of 1-bromoalkyne took place simultaneously and competitively (Scheme 44) [68].



Scheme 44. Liu et al. (2012).

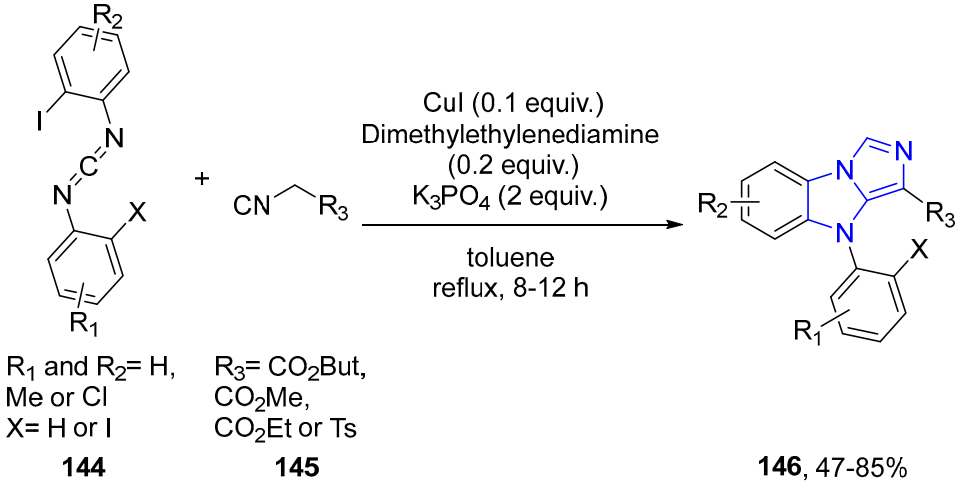
In 2012, Rosenberg and Clark demonstrated the total reaction protocol of pentosidine (**143**), an advanced glycation end product discovered as an extracellular protein cross-link. The total synthesis

was achieved via a six-step sequence starting with 3-amino-2-chloropyridine **142** and featuring a palladium-catalyzed tandem cross-coupling/cyclization to generate the imidazo[4,5-*b*]pyridine core (Scheme 45) [69].



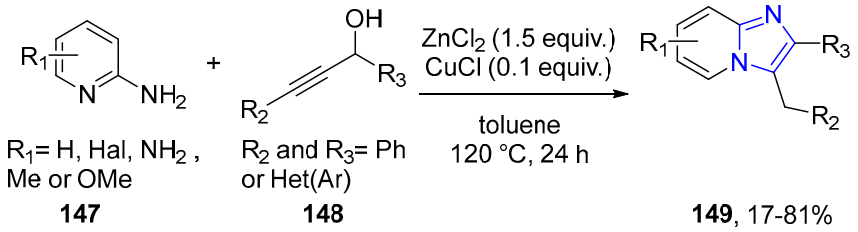
Scheme 45. Rosenberg and Clark (2012).

Qiu and Wu described the generation of benzoimidazo[1,5-*a*]imidazoles **146** via a copper-catalyzed tandem reaction. In this approach, the carbodiimides **144** reacted with isocyanides **145** catalyzed by copper(I) iodide, leading to benzoimidazo[1,5-*a*]imidazoles **146** and proceeded through a formal [3+2] cycloaddition and C–N coupling (Scheme 46) [70].



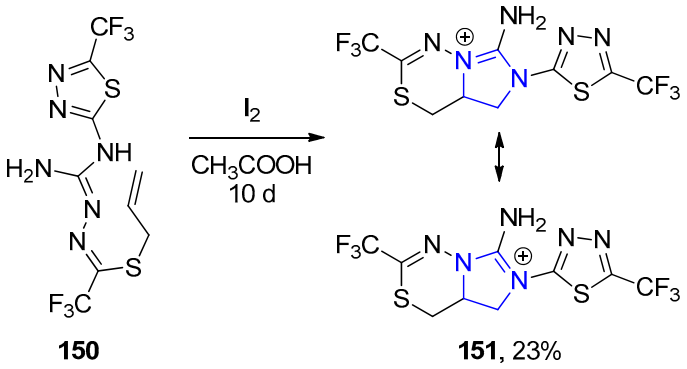
Scheme 46. Qiu and Wu (2012).

The team of Liu reported a tandem amination/cycloisomerization of aryl propargylic alcohols **148** with 2-aminopyridines **147** to synthesize imidazo[1,2-*a*]pyridines. They developed a $ZnCl_2$/CuCl system to achieve the direct amination and their subsequent intramolecular cycloisomerization (Scheme 47) [71].



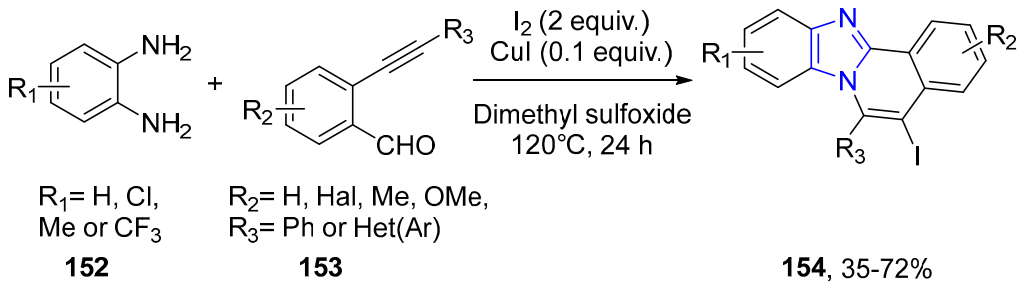
Scheme 47. Liu et al. (2011).

In 2011, Kim et al. reported a little study to obtain imidazo[1,5-*d*][1,3,4]thiadiazines **151**. The reaction was performed with iodine and accompanied by a tandem closure of heterocyclic systems **150** (Scheme 48) [72].



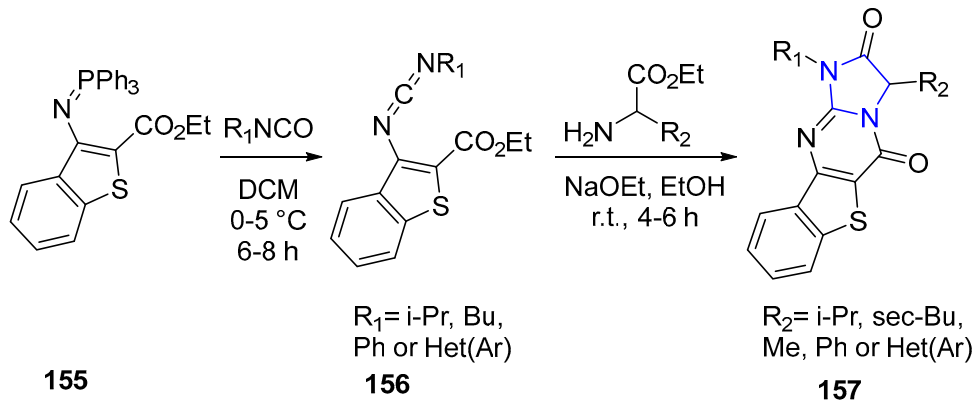
Scheme 48. Kim et al. (2011).

Ouyang and co-workers developeda protocol for the synthesis of iodoisoquinoline-fused benzimidazoles **154** by a tandem approach. In the presence of CuI, a variety of 2-ethynylbenzaldehydes **153** reacted with various benzenediamines **152** and iodine to afford the corresponding benzimidazoles in good yields. The protocol reported allowed the formation, through electrophilic annulation, of two heterocyclic rings in a one-pot reaction (Scheme 49) [73].



Scheme 49. Ouyang et al. (2011).

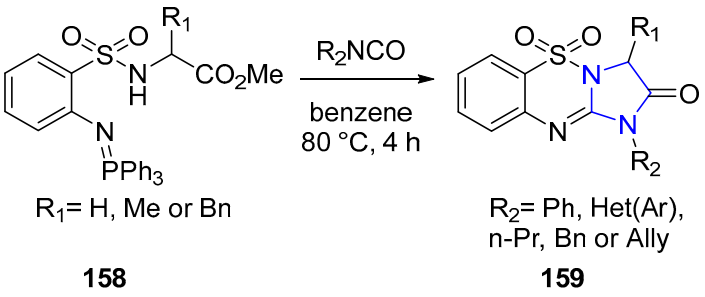
In 2010, Xu and co-workers employed a tandem aza-Wittig/heterocumulene-mediated annulation to accessbenzothieno[3,2-*d*]-imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-diones. Carbodiimide **156**, generated from the aza-Wittig reaction of iminophosphorane **155** with diverse aromatic isocyanate, reacted with the *α*-amino ester to give selectively tetracyclic **157** in the presence of a catalytic amount of sodium ethoxide (Scheme 50) [74].



Scheme 50. Xu et al. (2010).

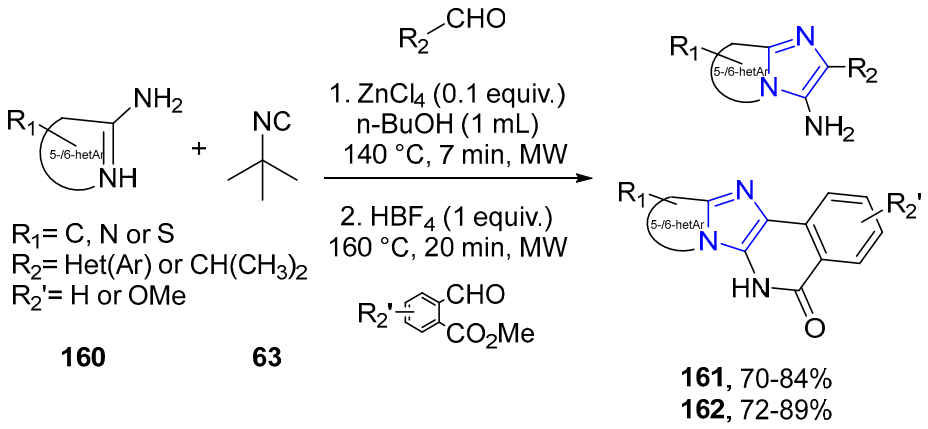
Hirota and collaborators designed sequential ring closure methodologies to synthesize imidazo benzo-1,2,4-benzothiadiazine-1,1-dioxide **159** and quinazolinone derivatives (Scheme 51) [75]. The protocol involved a one-pot synthetic method for diazaheterocyclic ring-closure via the tandem

aza-Wittig reaction/intramolecular NH-nucleophilic addition/NH-nucleophilic substitution cyclization, mediated by the sulfonamide ester–carbodiimide bifunctions.



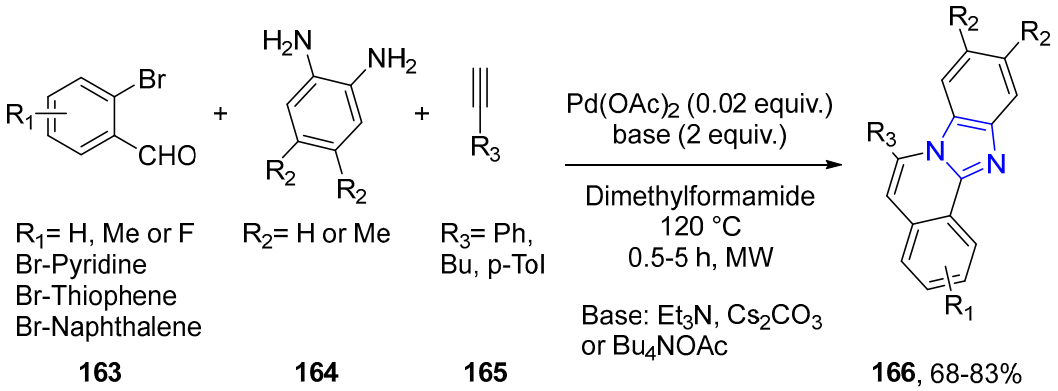
Scheme 51. Hirota et al. (2010).

Guchhait and Madaan developed the tandem dealkylation of derived tert-butyl amine in the one-step Ugi-type multicomponent reaction (MCR) product (Scheme 51). The tert-butyl isocyanide is a useful convertible isonitrile affording one-pot preparation of diverse polycyclic N-fused heterocycles including N-fused imidazole-amines **161** and tetracyclic heterocycles **162**. These compounds are therapeutically relevant core structures (Scheme 52) [76].



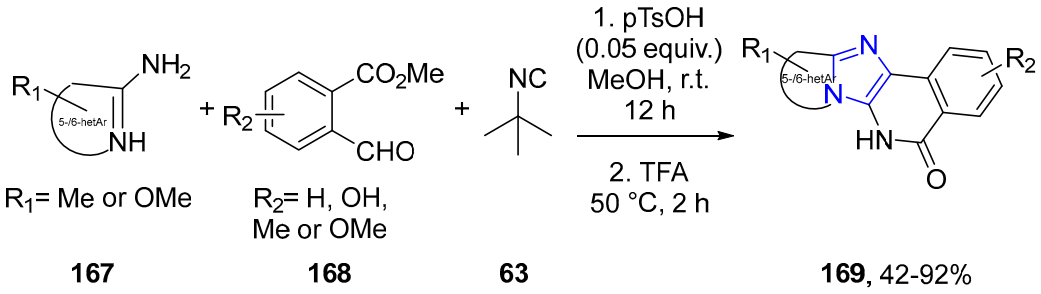
Scheme 52. Guchhait and Madaan (2010).

In 2009, Okamoto et al. reported an efficient methodology for the construction of the benzimidazo[2,1-*a*]isoquinoline ring system **166** from 2-bromoarylaldehydes **163**, 1,2-phenylenediamines **164**, and terminal alkynes **165** via a microwave-accelerated tandem process (Scheme 53) [77]. This approach successfully involved imine formation, a copper-ligand-free Sonogashira reaction, 5-endo-trig cyclization, oxidative aromatization, and 6-endo-dig cyclization.



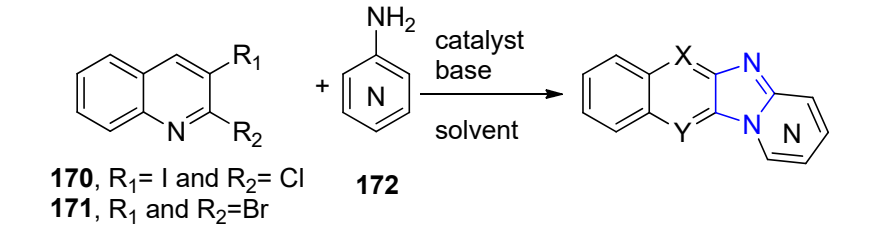
Scheme 53. Okamoto et al. (2009).

In 2007, the Che group adopted a tandem reaction to achieve quinoline-based tetracycles **169** (Scheme 54) [78]. The key step was a tandem three-component reaction of heteroaromatic amine **167**, methyl 2-formylbenzoates **168,** and t-butyl isonitrile **63**, followed by TFA-mediated lactamization via intramolecular aminolysis of the adjacent ester.



Scheme 54. Che et al. (2007).

In the same year, the group of Loones reported the synthesis of imidazo[4,5-*b*]quinoline and their benzo and aza analogs. The group developed regioselective tandem metal-catalyzed aminations on dihaloquinolines with amino(benzo)(di)azines (Scheme 55) [79]. The team achieved two libraries via auto- (**173**) and orthogonal (**174**) tandem amination.

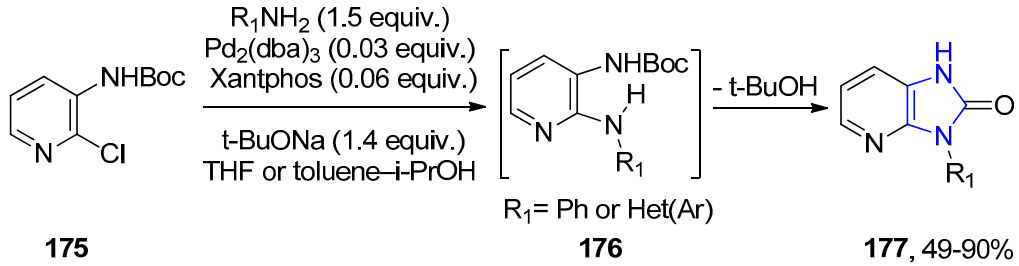


$Pd(OAc)_2$ (0.04 equiv.), *rac*-BINAP (0.04 equiv.) or Xantphos (0.04 equiv.), Cs_2CO_3 (4 equiv.), toluene, reflux,17 h : X=C and Y=N, **173**, 81-98%

$Pd_2(dba)_3$ (0.02 equiv.), Xantphos (4.4 mol %), CuI, Cs_2CO_3 (4 equiv.), DME,140 ºC, 24 h : X=N and Y=C, **174**, 14-90%

Scheme 55. Loones et al. (2007).

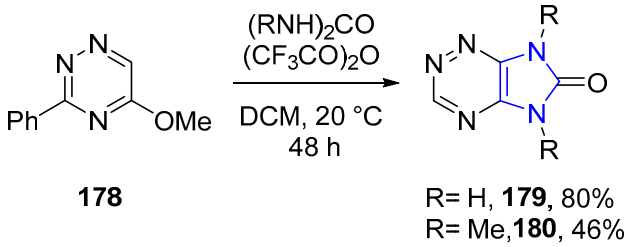
Scott described the two-step synthesis of 3-aryl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones **177** in good yields. For their preparation, a one-pot tandem palladium-catalyzed amination and intramolecular amidation of t-butyl (2-chloropyridin-3-yl)carbamate **175** with several substituted primary anilines was developed (Scheme 56) [80].



Scheme 56. Scott (2006).

The team of Beresnev published in 2000 atandem synthetic approach to obtain 6-azapurines. They reported access to imidazo[4,5-*e*]-1,2,4-trazines **179**–**180** from 5-methoxy-3-phenyl-1,2,4-triazine **178** and ureas in the presence of acylating agents (Scheme 57) [81]. The presence of an acylating agent

was a decisive factor. Trifluoroacetic anhydride was a stronger activator and played a crucial role in the aromatization of acylated compounds.



Scheme 57. Beresnev et al. (2000).

Final note on Imidazole: The bibliographic study of the synthesis approaches for the production of imidazoles using a tandem strategy revealed the use of different catalysts (Rh, I, Cu, Fe, or Ce). Iodine and Cu were applied in most cases.

4.2.3. Indole

Indole rings continue to be discovered in natural products and their interesting molecular architecture makes them suitable candidates for drug development (Figure 7). The presence of an indole nucleus in the amino acid tryptophan makes it an important heterocyclic system [2,22].

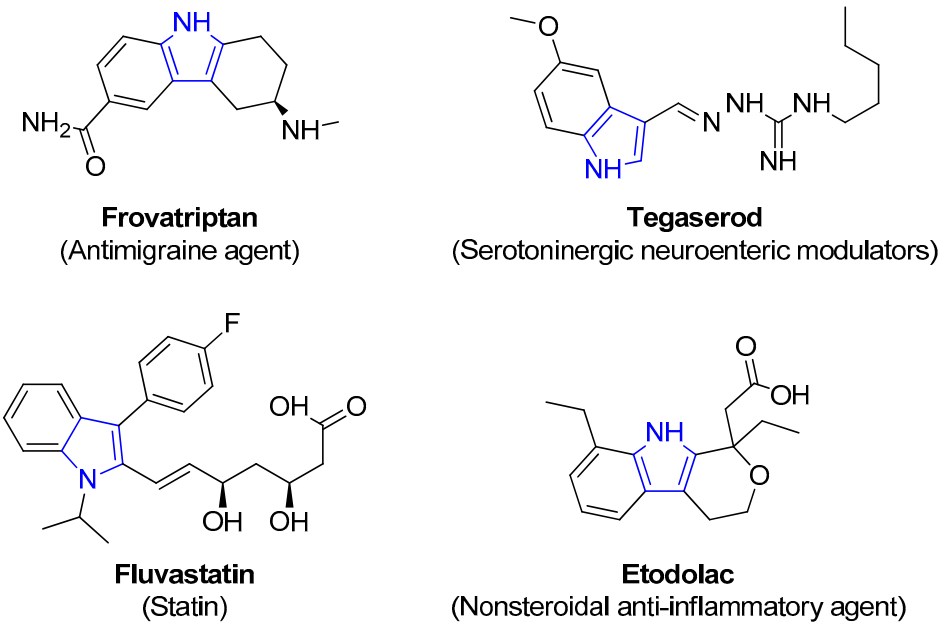
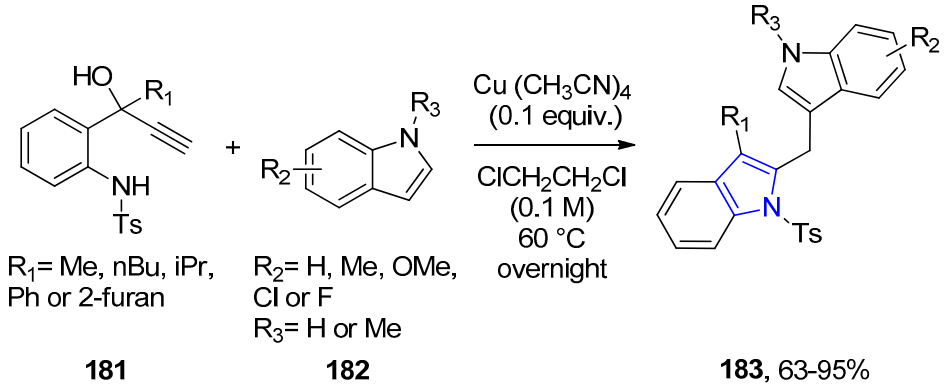


Figure 7. Drugs containing an indole ring.

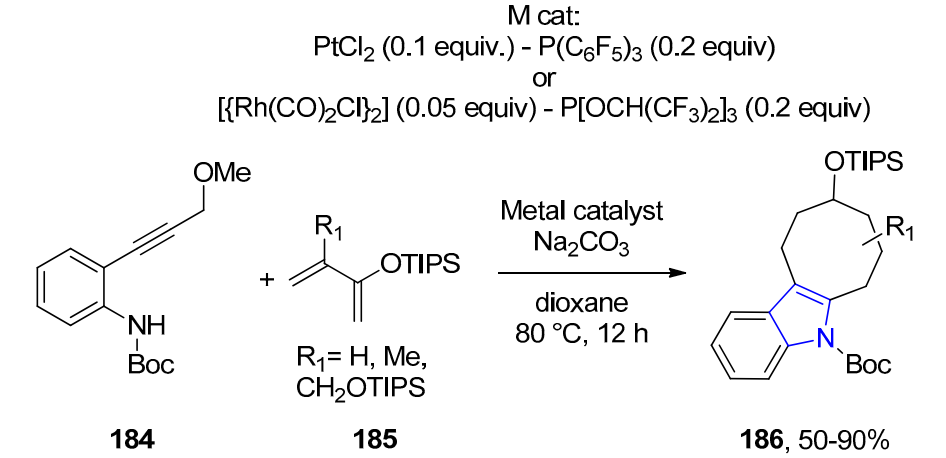
To the best of our knowledge, so far, only one team, that of Weiping Tang, has focused on the development of a tandem strategy to synthesize indole rings. The team published three studies between 2013 and 2014 [82–84].

In the most recent example, the library of diindolylmethanes **183** was achieved from propargylic alcohols **181** and indole nucleophiles **182** via a Cu-catalyzed tandem indole annulation/arylation reaction (Scheme 58) [82]. This team also assumed that indole nucleophiles could be replaced by other electron-rich arenes or alcohols.



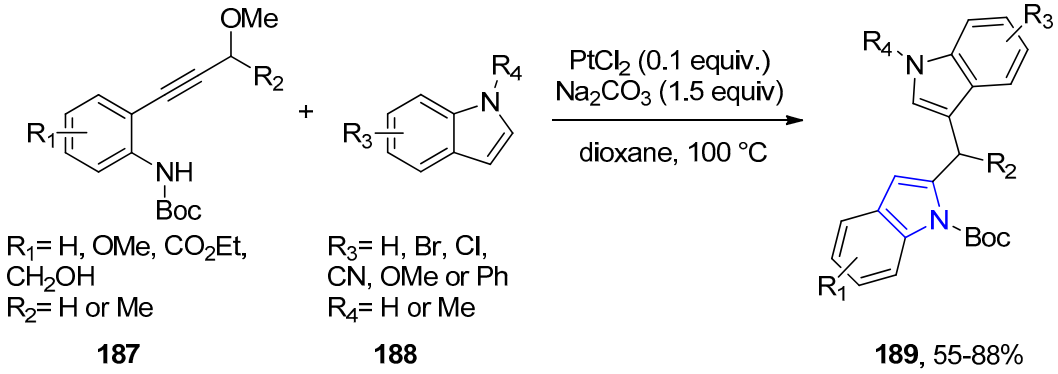
Scheme 58. Tang et al. (2014).

The group of Tang studied anindole annulation/[4+3] cycloaddition sequence for the synthesis of various substituted cyclohepta[*b*]indoles **186** using rhodium and platinum as catalysts(Scheme 59) [83]. Both acyclic and cyclic dienes participated in this tandem reaction, and high regio-selectivity was observed.



Scheme 59. Tang et al. (2013).

In the same year and again using platinum as a catalyst, Tang et al. reported the synthesis of diindolylmethanes **189** from propargylic ethers **187** and substituted indoles **188** via a platinum-catalyzed tandem indole annulation/arylation cascade (Scheme 60) [84].



Scheme 60. Tang et al. (2013).

Final note on Indole: For the synthesis of the indole ring using a tandem-catalyzed approach, three different catalysts were found: Cu, Pt, and Rh.

4.2.4. Tetrazole

Tetrazoles are a class of synthetic organic heterocyclic compounds with the highest nitrogen contents among the stable heterocycles. In the present review, we focus on studies reporting tetrazole achieved by a tandem procedure. The interesting tetrazole function is metabolically stable, and this feature and a close similarity between the acidic character of the tetrazole group and the carboxylic group have inspired its possible use for syntheses of potential medicinal agents (Figure 8) [2,22].

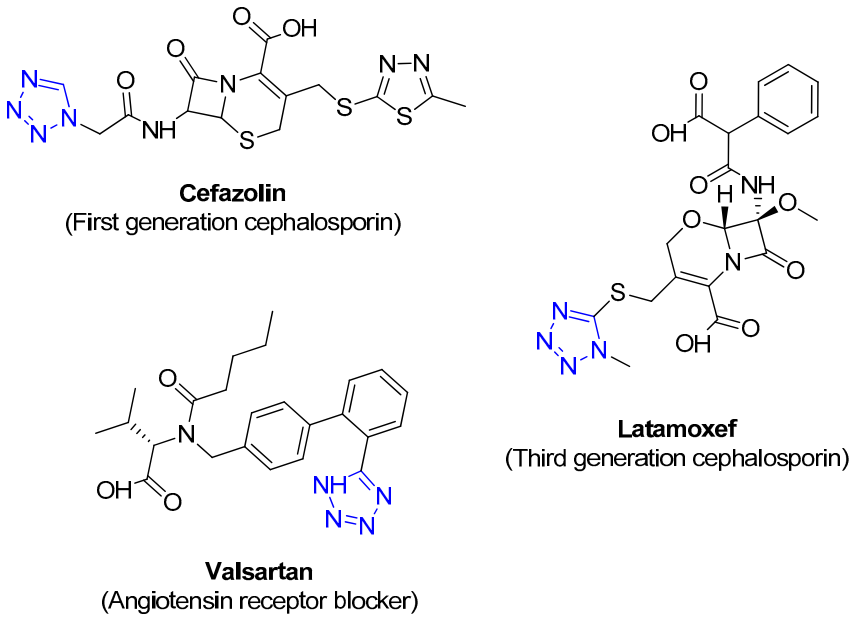
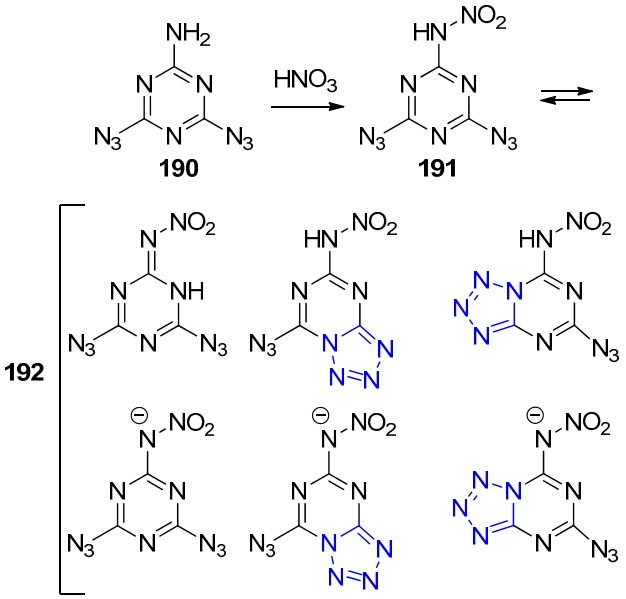


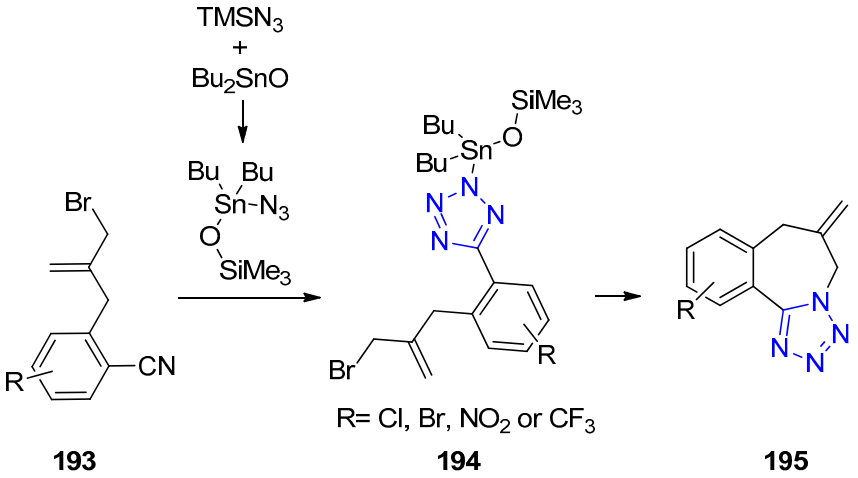
Figure 8. Drugs containing a tetrazole ring.

Chapyshev and Ushakov developed a theoretical study of tandem deprotonation/azide—tetrazole tautomerization of 4,6-diazido-*N*-nitro-1,3,5-triazin-2-amine **191** in dimethylsulfoxide solutions. The transformations **192** found may be of interest in their reaction with various electrophilic agents (Scheme 61) [85].



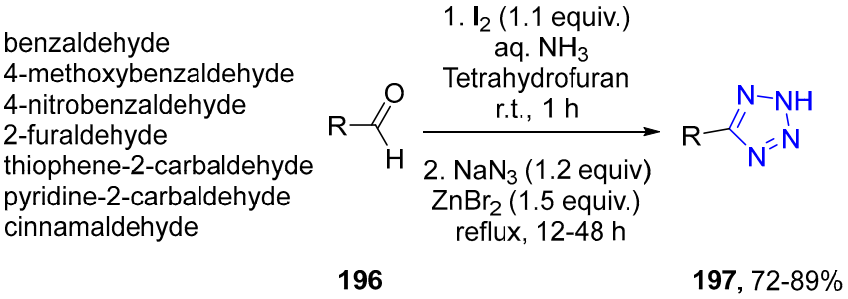
Scheme 61. Chapyshev and Ushakov (2015).

Ek et al. synthesized fused tricyclic tetrazoles **195** from allylic bromides performed by the DiazAll reaction. This tandem procedure comprised a cycloaddition between a nitrile and Azidotrimethylsilane ($TMSN_3$) induced by dibutyltin oxide (DBTO) and followed by an intramolecular N-allylation (Scheme 62) [86].



Scheme 62. Ek et al. (2004).

Shie and Fang adopted a one-pot tandem reaction for the direct conversion of substituted benzaldehydes and heterocyclic aromatic aldehydes **196** to 5-aryltetrazoles **197** with I_2/aq NH_3 at room temperature and $NaN_3/ZnBr_2$ at reflux (Scheme 63) [87]. This protocol was conducted smoothly in aqueous media, and the desired products were obtained simply by extraction or filtration.



Scheme 63. Shie and Fang (2003).

Final note on Tetrazole: In the three studies found in the literature for the formation of the tetrazole ring, only the use of iodine was reported.

4.2.5. Triazole

The triazole ring is one of the most important heterocycles and has been found in the structure of various natural products and pharmaceutical drugs (Figure 9) [2,22]. This review may help medicinal chemists to develop new leads possessing a triazole ring as a linker between two molecules, or embedded in a polyheterocycle, using a tandem approach.

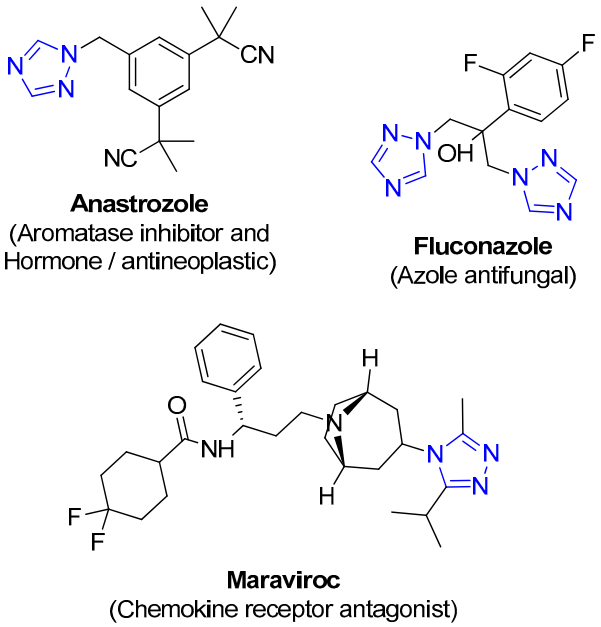
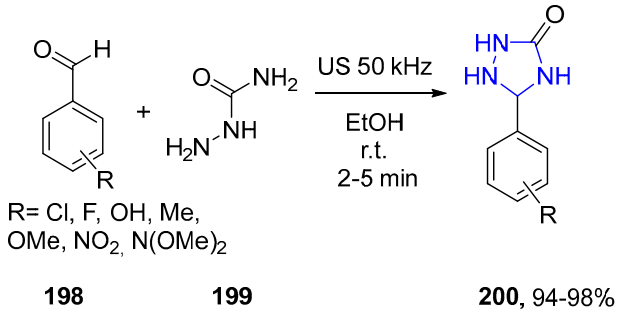


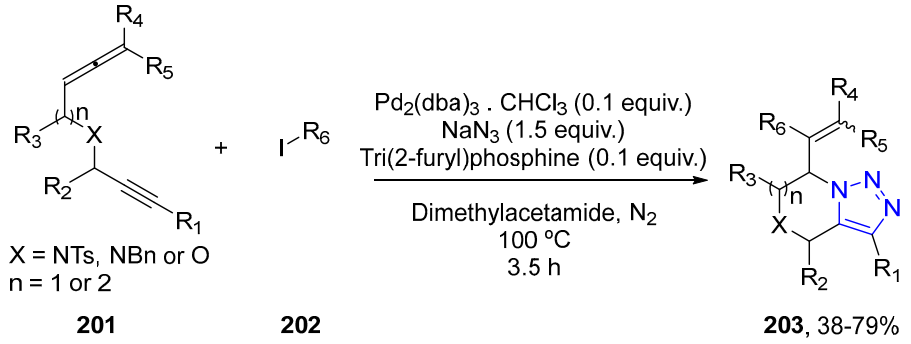
Figure 9. Drugs containing a triazole ring.

Jonnalagadda et al. established an efficient ultrasonic-assisted one-pot tandem protocol for the synthesis of triazole derivatives **200** with excellent yields. The desired products were obtained via single-step tandem (Knoevenagel-cyclic condensation) reactions of aldehydes **198** and semicarbazide **199** in ethanol in the absence of a catalyst at room temperature (Scheme 64) [88].



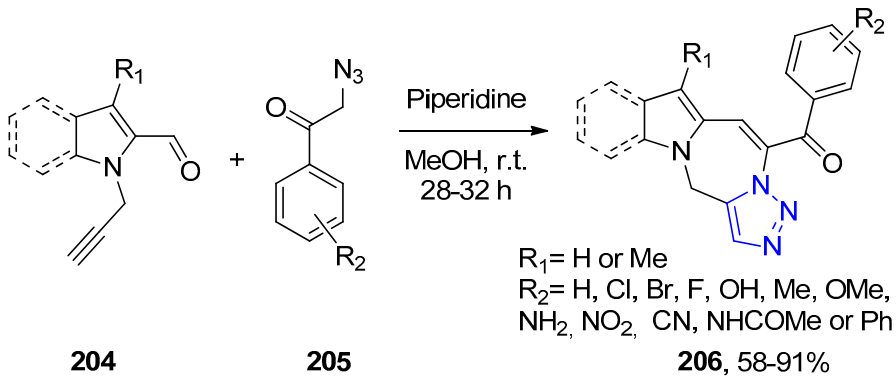
Scheme 64. Jonnalagadda et al. (2020).

Ma et al. demonstrated a practical method for the construction of [4.3.0]-bicyclic 1,2,3-triazole derivatives **203** via a palladium-catalyzed three-component tandem reaction of allenynes **201**, organic iodides **202**, and NaN_3. The reaction resulted from a cascade allene difunctionalization/Winstein allylic azide rearrangement/intramolecular azide-alkyne cycloaddition route (Scheme 65) [89].



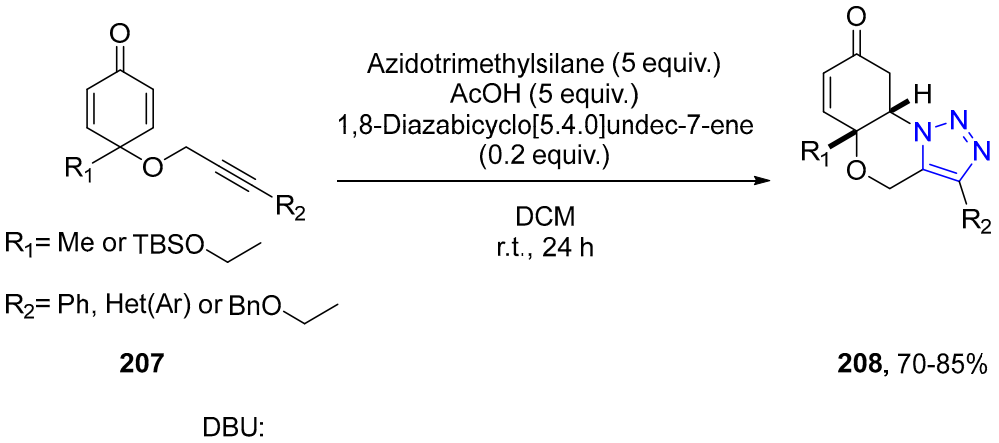
Scheme 65. Ma et al. (2019).

Nanduri et al. designed an approach for the synthesis of fused 1,2,3-triazole indolo- and pyrrolodiazepine derivatives **206** via a tandem pathway of an initial Knoevenagel condensation followed by azide–alkyne 1,3-dipolar cycloaddition at room temperature with good to high yields (Scheme 66) [90].



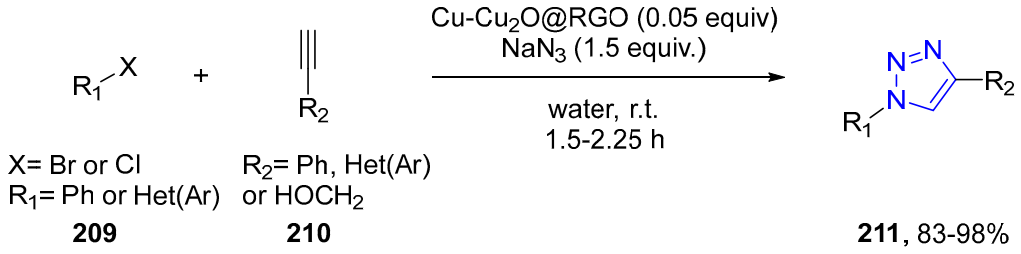
Scheme 66. Nanduri et al. (2019).

Chandrasekhar et al. accomplished a metal-free domino β-azidation/[3+2] cycloaddition under room temperature with good yields for the synthesis of 1,2,3-triazole-fused dihydrobenzoxazinons **208**.The team obtained cis-fused triazoles containing dihydrobenzoxazenones from a varied scope of alkynylated cyclohexa 2,5-dienones (Scheme 67) [91].



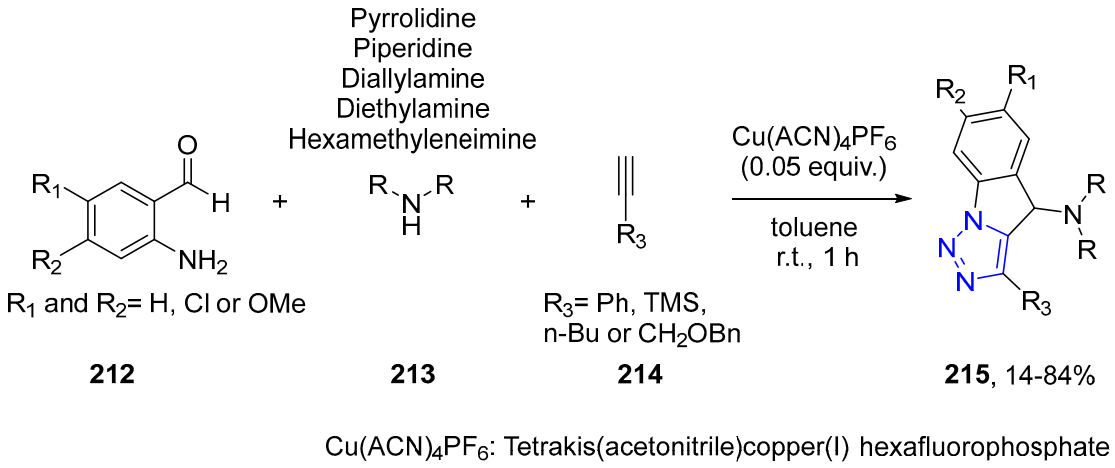
Scheme 67. Chandrasekhar et al. (2019)

Chu et al. performed tandem reactions of halides and sodium azide with various terminal alkynes to synthesize 1,4-disubstituted 1,2,3-triazoles **211** using a catalyst developed by the team (Scheme 68). Cu-Cu_2O@RGO as a heterogeneous catalyst showed excellent recyclability performance, good separation, and high stability in the tandem process for the synthesis of 1,2,3-triazole compounds [92].



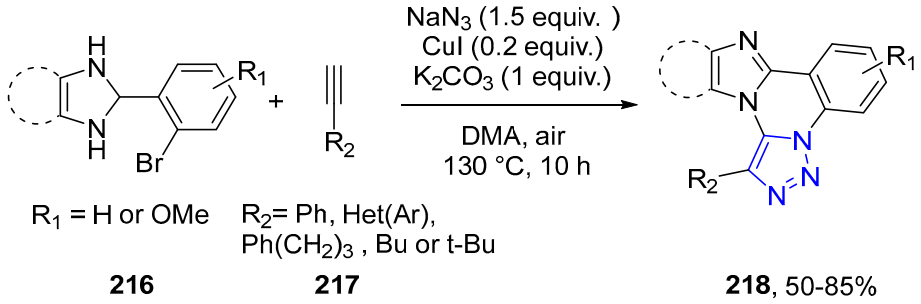
Scheme 68. Chu et al. (2018).

Boobalan et al. accomplished the desired product **215** by the A3 coupling reaction of various benzaldehydes **212**, secondary amines **213**, and terminal alkynes **214** in toluene at room temperature. All substrates produced the corresponding 4-amino-4*H*-triazoloindole products in good yields. However, with acyclic secondary amines, the yields were lower. This methodology for the formation of 3-aryl/alkyl/silyl-4-amino-4*H*-triazoloindoles via a Cu(I)-mediatedtandem A3 coupling/[3+2] cycloaddition reaction was developed successfully (Scheme 69) [93].



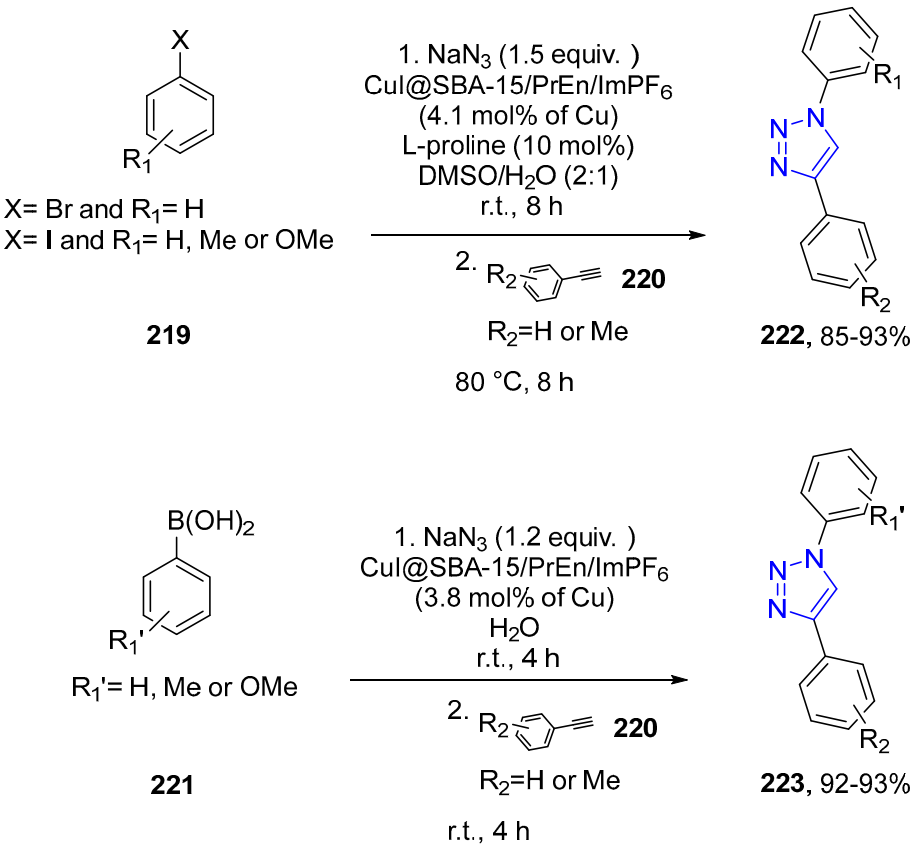
Scheme 69. Boobalan et al. (2018).

Nandwana and co-workers carried out a copper-catalyzed tandem reaction from 2-(2-bromo-aryl) imidazoles/2-(2-bromoaryl)benzimidazoles **216**, alkynes **217**,and sodium azide. This methodology involved the well-known copper-catalyzed azide–alkyne cycloaddition (CuAAC), followed by intramolecular cross-dehydrogenative C–N bond formation, and anUllmann-type C–N coupling was then allowed to close the sequence, the air serving as oxidant. The team also declared that the conditions applied for the synthesis of imidazo-[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines **218** can be performed with high efficiency with a wide range of substrates (Scheme 70) [94].



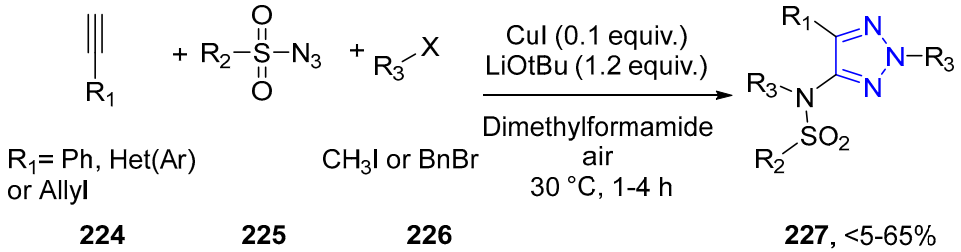
Scheme 70. Nandwana et al. (2017).

Hosseini and co-workers described a tandem approach for the synthesis of triazoles using CuI@SBA-15/PrEn/ImPF6 as a catalyst. The catalyst developed showed high activity, high stability, and no appreciable leaching of CuI, owing to its strong binding via the coordination with PrEn functionality. This catalyst was successfully applied in tandem methods for the synthesis of 1,4-diphenyl-1*H*-1,2,3-triazole **222**, **223** from different substrate pairs: Either aryl halides **219** and aryl acetylenes **220** or arylboronic acids **221** and aryl acetylenes **220**, under aqueous conditions in excellent yields (Scheme 71) [95].



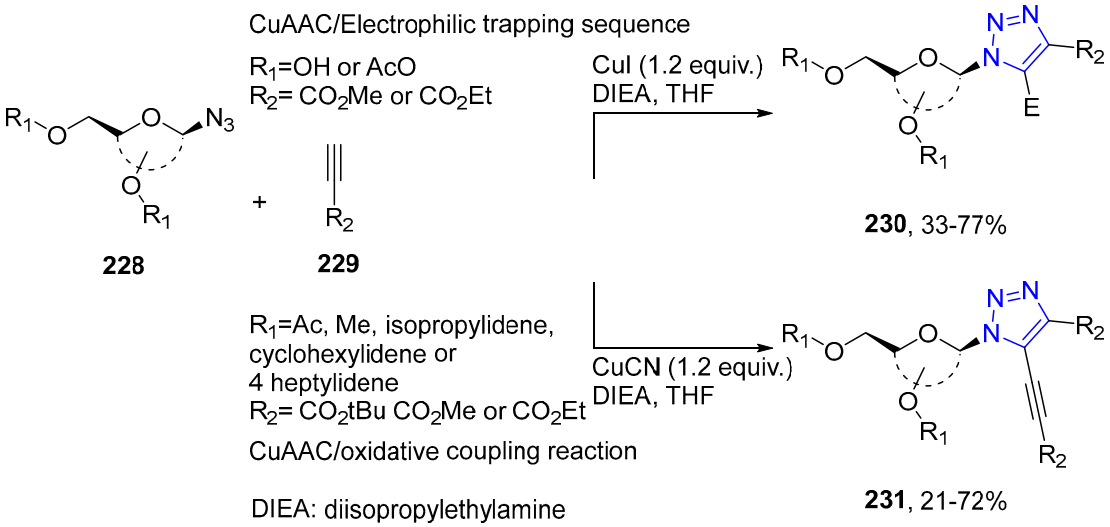
Scheme 71. Hosseini et al. (2017).

Zheng et al. obtained 5-sulfamide-1-(*N*-sulfonyl)-1,2,3-triazoles **227** via the tandem Huisgen [3+2] cycloaddition/amidation reaction of terminal alkynes **224** and sulfonyl azides **225**. The Zheng group developed direct access to 5-sulfamide-1-(*N*-sulfonyl)-1,2,3-triazoles in high chemo- and regioselectivity using copper-catalyzed conversion of sulfonyl azides and terminal alkynes with stoichiometric amounts of LiO^{t}Bu in DMF at 30 °C under air atmosphere (Scheme 72) [96].



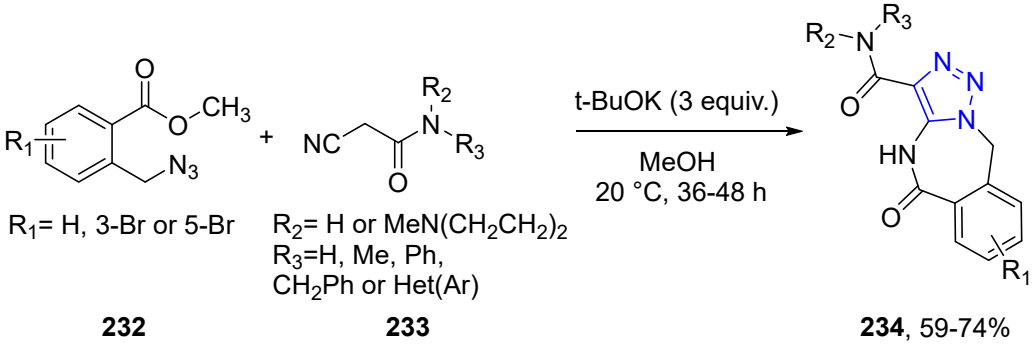
Scheme 72. Zheng et al. (2017).

The Amdouni group performed tandem procedures for the synthesis of 1,4,5-trisubstituted-1,2,3-triazole using click/electrophilic addition **230** or click/oxidative coupling strategies **231** (Scheme 73) [97].



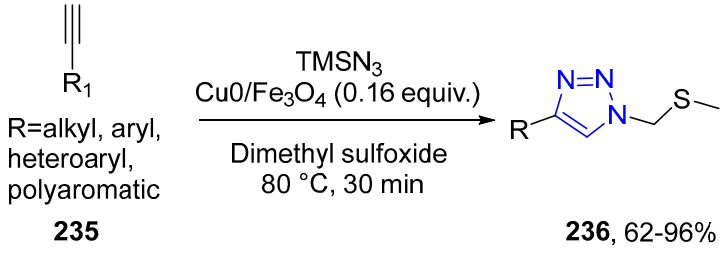
Scheme 73. Amdouni et al. (2017).

Yakovenko and co-workers attained triazolo[1,5-*b*][2,4]benzodiazepine **234** by tandem cyclization. The derivatives were achieved successfully from tandem anionic cyclization of o-(azidomethyl) benzoates **232** with 2-cyanoacetamides **233** (Scheme 74) [98].



Scheme 74. Yakovenko et al. (2017).

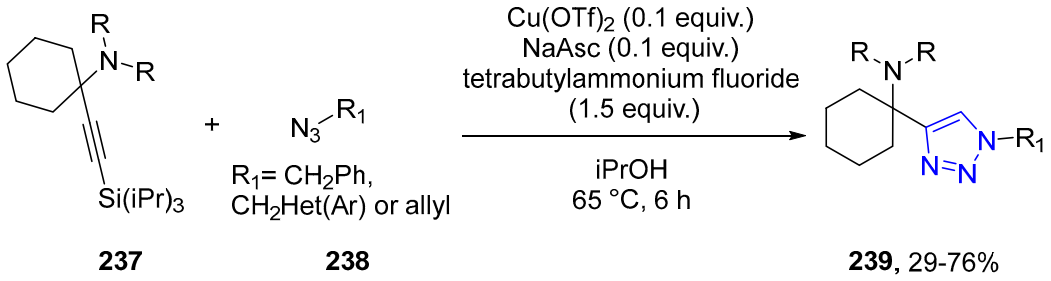
Phanindrudu et al. carried out a tandem nano Cu0/Fe_3O_4-catalyzed reaction of terminal alkynes **235** and trimethylsilyl azide. In this procedure developed to synthesize sulfur-containing triazoles **236**, the trimethylsilyl azide and dimethyl sulfoxide acted as nitrogen and sulfur sources, respectively. The authors showed that the catalyst was magnetically recovered and can be reused six times without any significant loss of activity (Scheme 75) [99].



Scheme 75. Phanindrudu et al. (2016).

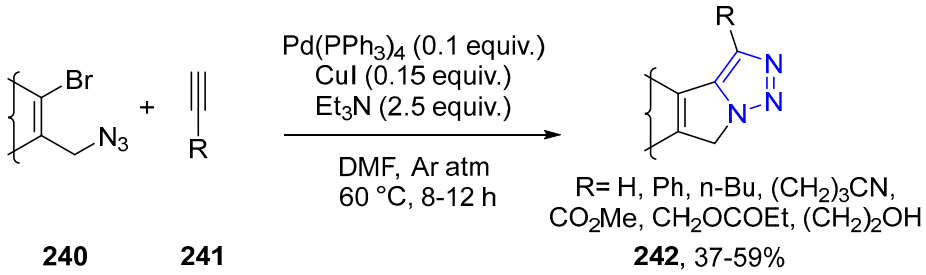
The team of Palchak performed a tandem copper-catalyzed silyl deprotection/azide cycloaddition to access alpha-tetrasubstituted triazole derivatives **239** from propargylamines **237**. The better activity of copper(II) triflate in the formation of triazoles from sensitive alkyne substrates was effectively

extended to simple terminal alkynes. The catalyst combination of copper(II) triflate and sodium ascorbate allowed the use of sensitive and hindered substrates (Scheme 76) [100].



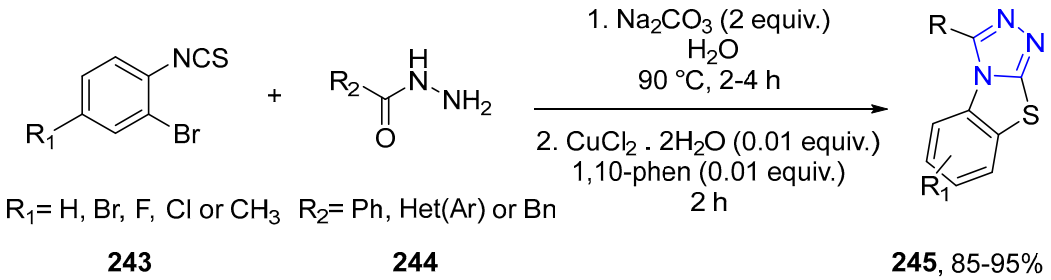
Scheme 76. Palchak et al. (2015).

The Rakshit group described a tandem Sonogashira coupling-CuAAC reaction to obtain some annulated 1,2,3-triazoles **242**. This protocol was applied successfully by the palladium(0)-copper(I)-catalyzed intramolecular heteroannulation of various 2-/1-azido-methyl-1-/2-bromodihydro-naphthalenes, -arene, and -cyclo alkenes **240** with some terminal alkynes **241** (Scheme 77) [101].



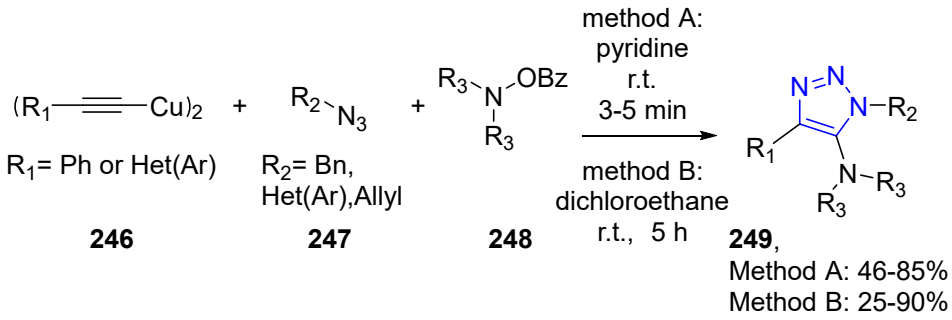
Scheme 77. Rakshit et al. (2015).

Wen and co-workers attempted and achieved benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazoles **245** via a tandem intermolecular C−N bond and intramolecular C−S bond formation sequence. The derivatives were prepared from *o*-bromo-arylisothiocyanates **243** and aroylhydrazides **244** under water with $CuCl_2 \cdot 2H_2O$/11,10-phenanthroline as the catalyst (Scheme 78) [102].



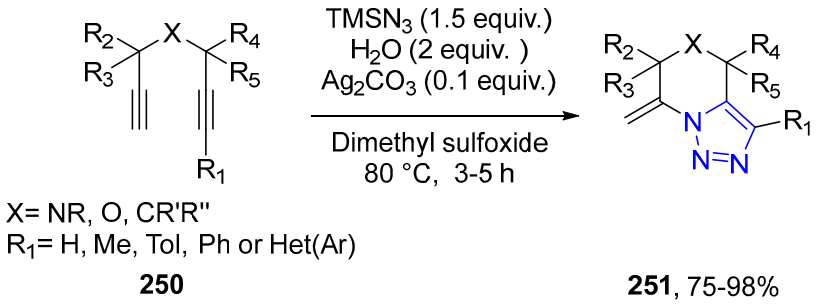
Scheme 78. Wen et al. (2015).

The Wang team achieved the synthesis of 1,4,5-trisubstituted 5-dialkylamino-1,2,3-triazoles **249** using a tandem approach. Various derivatives were obtained, at room temperature, from the reaction of 1-copper alkynes **246**, azides **247**, and *o*-benzoyl hydroxylamines **248** for only five minutes (Scheme 79) [103]. The authorsalso presented the results when the reaction was carried out in 1,2-dichloroethane for 5h.



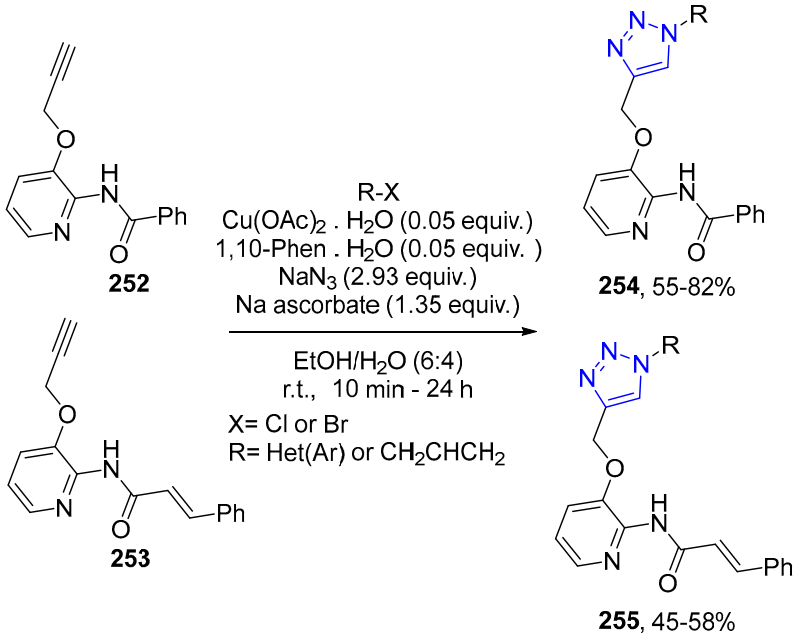
Scheme 79. Wang et al. (2015).

Ning and co-workers obtained a library offused 1,2,3-triazoles **251** by performing a tandem cyclization of diynes **250** with $TMSN_3$ and silver catalysis in the presence of H_2O. This protocol involved a cascade hydroazidation and alkyne−azide 1,3-dipolar cycloaddition of diynes, and it was shown to be compatible with a broad substrate scope and have a good functional group tolerance and high efficiency (Scheme 80) [104].



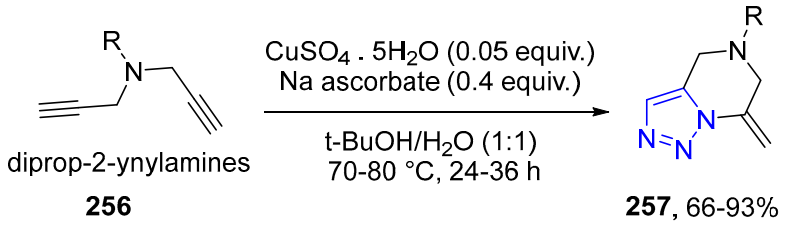
Scheme 80. Ning et al. (2015).

The group of Verma reported the successful construction of several 1,2,3-triazole-containing pyridines **254**–**255** by performing one-pot tandem copper-catalyzed azidation and CuAAC reaction from sodium azide and the corresponding halides (Scheme 81) [105].



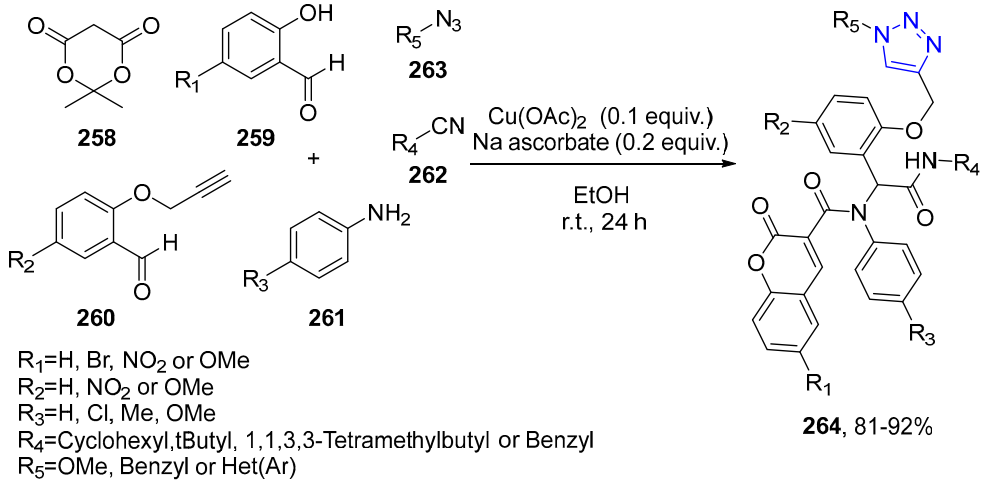
Scheme 81. Verma et al. (2015).

Roy et al. achieved the synthesis of tetrahydro[1,2,3]triazolopyrazines **257** in mixed aqueous–organic media by employing a one-pot 1,3-dipolar cycloaddition reaction followed by a tandem intramolecular 6-exo-dig cycloaddition reaction. The construction of triazole-fused pyrazines was prepared with several amino acids and primary amines **256**. The authors pointed out that the method reported was limited to substrates bearing terminal alkynes (Scheme 82) [106].



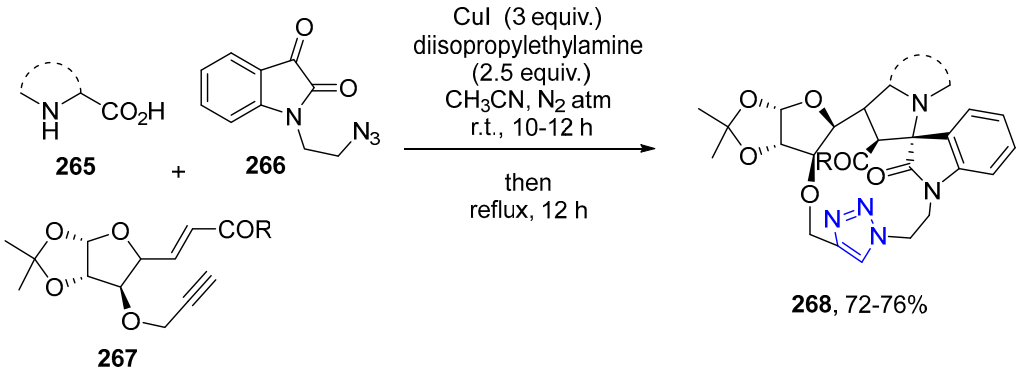
Scheme 82. Roy et al. (2014).

Shaabani and co-workers described the synthesis of trifunctional coumarin-amide-triazole containing compounds **264** via a one-pot tandem Knoevenagel/Ugi/click reaction, six-component sequence (**258**–**263**), from readily available starting materials at room temperature in ethanol in excellent overall yields. This methodology involved the preparation in situ of coumarin-3-carboxylic acid and a terminal triazole ring (Scheme 83) [107].



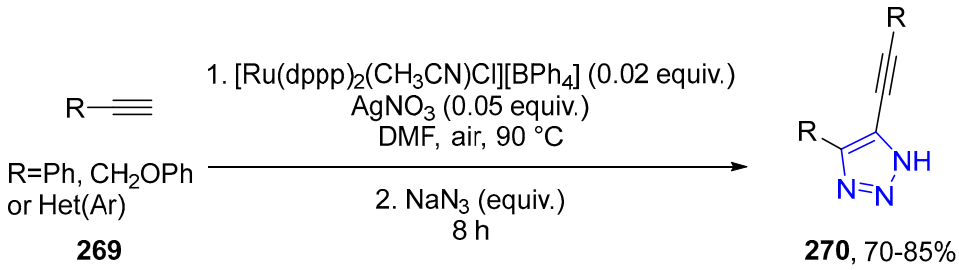
Scheme 83. Shaabani et al. (2014).

The Prasanna team introduced a tandem double 1,3-dipolar cycloaddition reaction for the synthesis of heterocycle-grafted sugar macrocycles **268**. The team developed triazole-linked macrocycles grafted with a glycospiro heterocycle using a stereo and regioselective tandem approach (Scheme 84) [108].



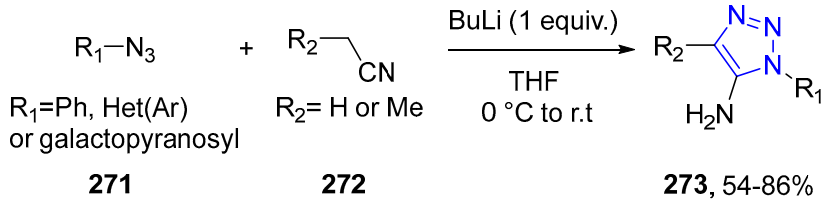
Scheme 84. Prasanna et al. (2014).

Das and co-workers generated a $[Ru(dppp)_2Cl][BPh_4]$ complex to catalyze a homocoupling reaction of alkynes and subsequent tandem alkyne–azide cycloaddition. The ruthenium complex was successfully used for the one-pot synthesis of 4-substituted-5-alkynyl-1,2,3-trazoles **270** (Scheme 85) [109].



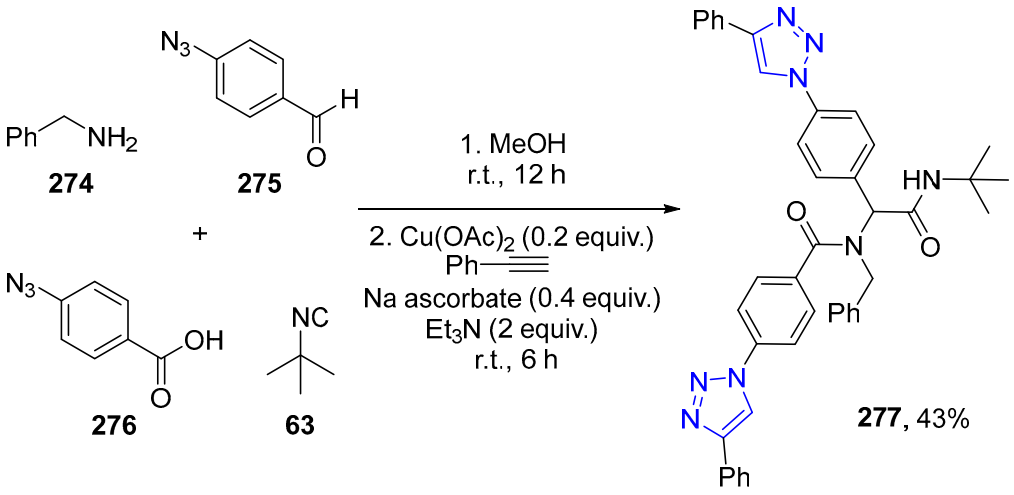
Scheme 85. Das et al. (2014).

Gomes et al. prepared 5-amino-1*H*-1,2,3-triazoles **273** using a tandem cycloaddition between azides **271** and nitriles **272** in THF at room temperature (Scheme 86) [110].



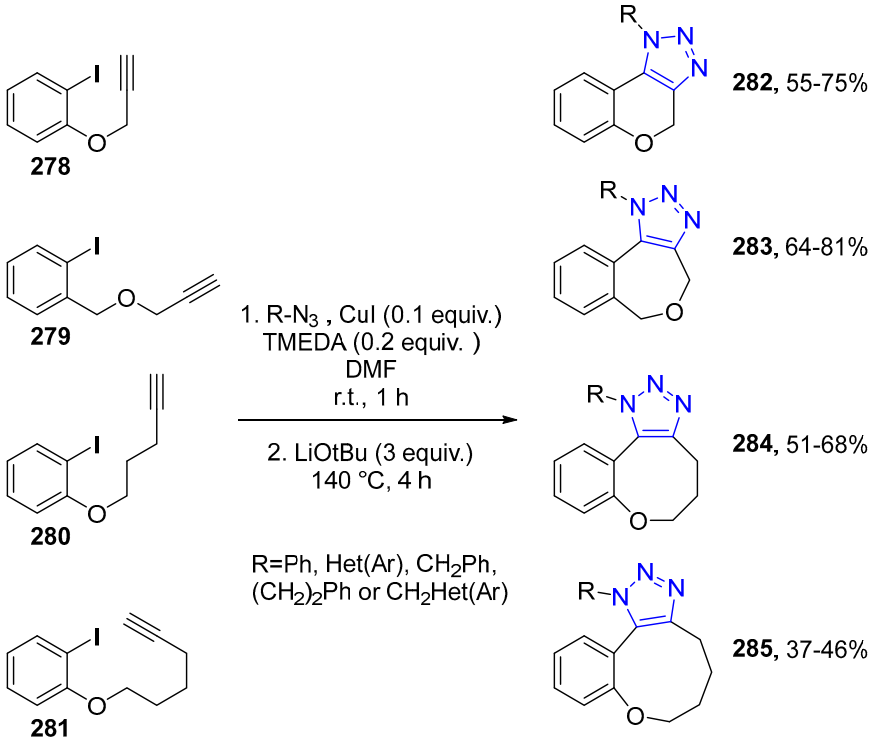
Scheme 86. Gomes et al. (2013).

Niu and co-workers monitored a classical one-pot tandem Ugi multicomponent reaction (MCR)/click reaction sequence not requiring protecting groups. Several 1*H*-1,2,3-triazole-modified Ugi-reaction products were synthesized successfully [111]. Encouraged by these results, the team attempted to carry out the analogous reaction with azidobenzaldehyde **275** and azidobenzoic acid **276** in one pot; benzylamine (**274**) and tert-butyl isocyanide (**63**) were used to form the amide of the amino acid moiety of the triazole-modified Ugi-reaction product. Thus, a triazole-modified Ugi-reaction product **277** containing two 1*H*-1,2,3-triazole units in both the terminal and side-chain positions was successfully synthesized (Scheme 87).



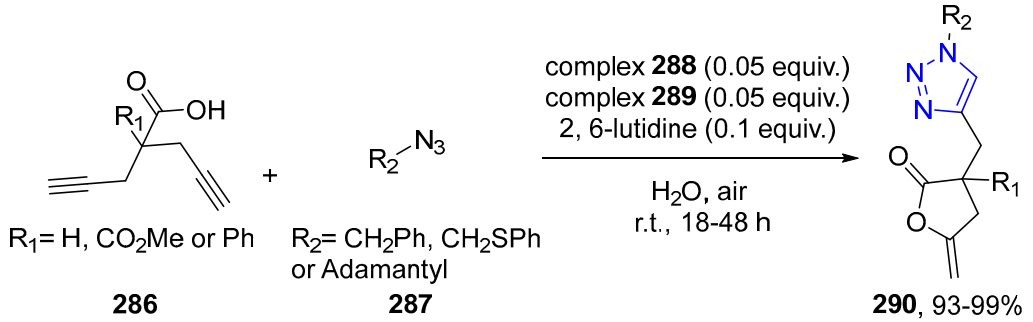
Scheme 87. Niu et al. (2012).

Reddy and Swamy managed a route to the construction of [6,6]-, [6,7]-, [6,8]-, and [6,9] ring-fused triazoles **282–285** by copper-catalyzed, tandem, one-pot click and intramolecular arylation reactions. This procedure used two distinct mechanisms: First one was the well-known atom-economical click reaction and the second was the direct arylation of 1,2,3-triazole. Furthermore, the difference of reactivity between the fused triazoles prepared from 2-bromobenzyl azide and 2-bromophenyl azide led to a fused pentacyclic heterocycle for the former and a C–C-coupled, biphenyl-fused, tricyclic product for the latter under Pd catalysis (Scheme 88) [112].



Scheme 88. Reddy and Swamy (2012).

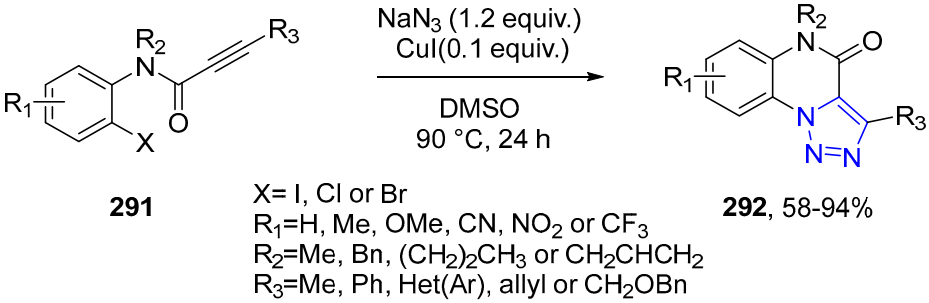
The group of García-Álvarez prepared triazol-enol-lactones **290** via a one-pot tandem orthogonal reaction. The protocol developed in water was catalyzed using two complexes: Trans-[$PdCl_2${μ_2-N,S-(PTA)=NP(=S)$(OEt)_2$}]$_2$(**288**) and [Cu{μ_2-N,S-(-(PTA)=NP(=S)$(OEt)_2$}]x[SbF_6]x (**289**). The reaction to synthesize bicyclic triazol-enol-lactones was conducted at room temperature under aerobic conditions and involved the cycloisomerization of γ-alkynoic acids, followed by a 1,3-dipolar cycloaddition of azides **287** with terminal alkynes **286** (Scheme 89) [113].



Scheme 89. García-Álvarez et al. (2012).

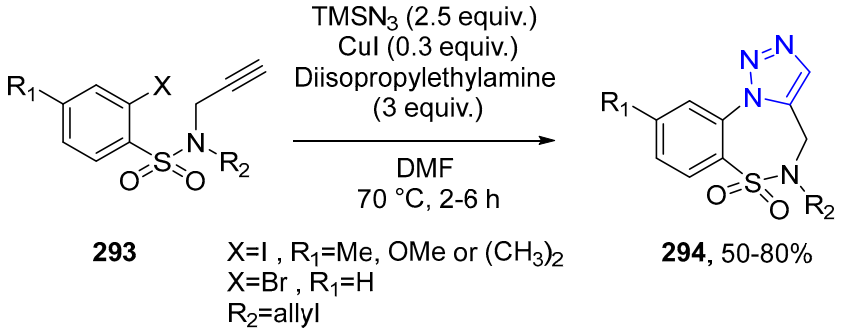
Yan and co-workers carried out the preparation of [1,2,3]triazolo-[1,5-*a*]quinoxalin-4(5*H*)-ones **292** through a copper-catalyzed tandem approach. The methodology was based on the copper-promoted

reaction of a variety of 1-(2-haloaryl)propamides **291** with sodium azide via a tandem azide alkyne cycloaddition/Ullmann CN coupling process (Scheme 90) [114].



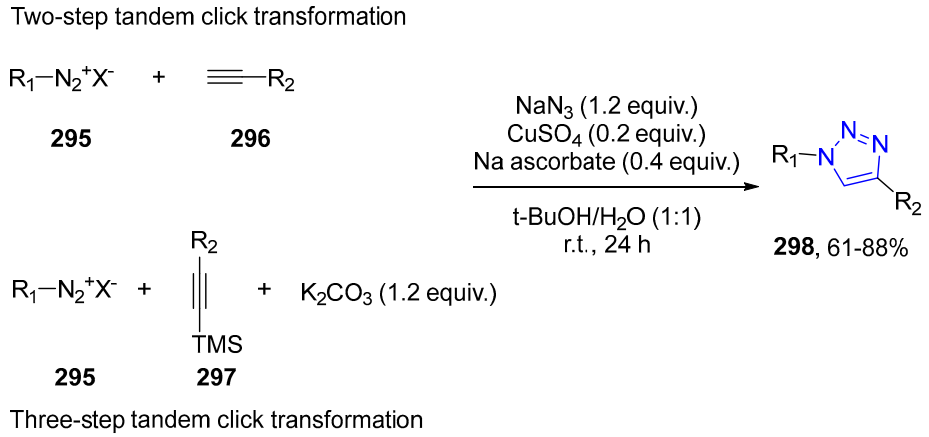
Scheme 90. Yan et al. (2012).

The Barange team obtained triazolothiadiazepine-1,1-dioxide derivatives **294** via copper-catalyzed [3+2] cycloaddition, followed by N-arylation. The synthetic route studied was successfully used to also synthesize indoline- and thiophene-fused triazolothiadiazepine 1,1-dioxide derivatives in moderate to good yields (Scheme 91) [115].



Scheme 91. Barange et al. (2011).

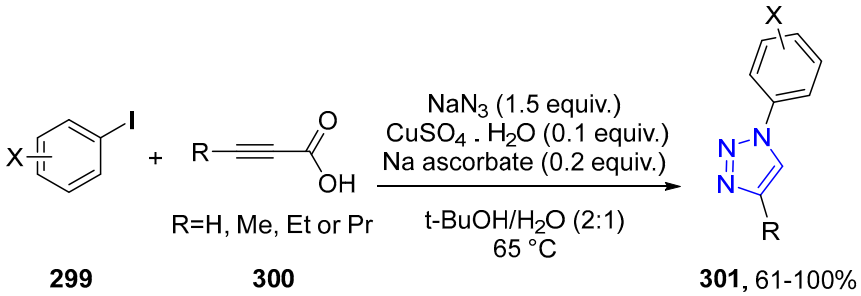
Fletcher and Reilly employed two-step one-pot tandem reactions with terminal alkynes **296** and three-step one-pot tandem reactions with trimethylsilyl-protected alkynes **297** to prepare 1,2,3-triazole derivatives **298**. The various azidoarenes were achieved under click reaction conditions of $CuSO_4$/Na ascorbate catalyst with a 1:1 t-BuOH/H_2O mixture as solvent (Scheme 92) [116].



Scheme 92. Fletcher and Reilly (2011).

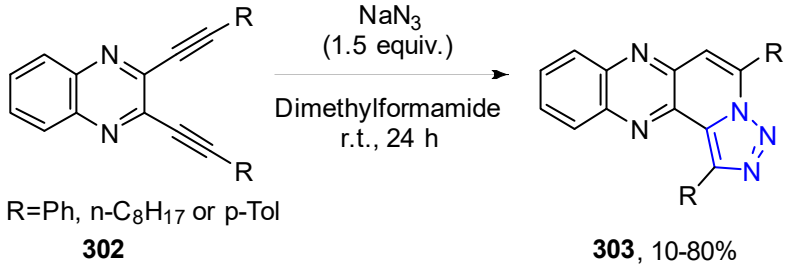
Kolarovic et al. investigated a decarboxylative Cu(I)-catalyzed azide alkyne cycloaddition under tandem catalysis conditions. The methodology involved the decarboxylative coupling of alkynoic

acids **300** and 1,3-dipolar cycloaddition of azides, enabling a highly efficient production of a variety of functionalized 1,2,3-triazoles **301**. The three-step, one-pot method avoided the use of highly volatile terminal alkynes, reduced the handling of often unstable and sometimes explosive azides to a minimum, and furnished the target structures in excellent purity and yields (Scheme 93) [117].



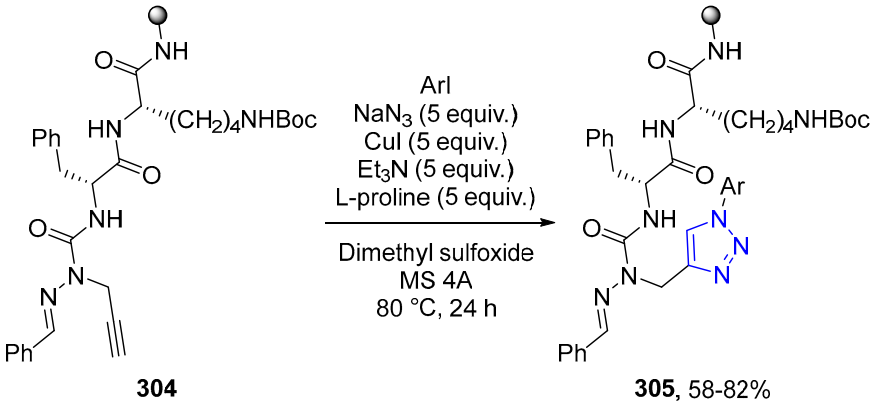
Scheme 93. Kolarovic et al. (2011).

Gulevskaya and co-workers demonstrated a possible tandem cyclization of 2,3-dialkynylpyrazines **302** into [1,2,3]triazolo[1′,5′;1,2]pyrido[3,4-*b*]pyrazines **303** using sodium azide in DMF at room temperature. The reaction performed involved a 1,3-dipolar cycloaddition of an azide ion to the carbon–carbon triple bond followed by intramolecular nucleophilic addition of the generated intermediate 1,2,3-triazole N-anion to another C–C bond (Scheme 94) [118].



Scheme 94. Gulevskaya et al. (2010).

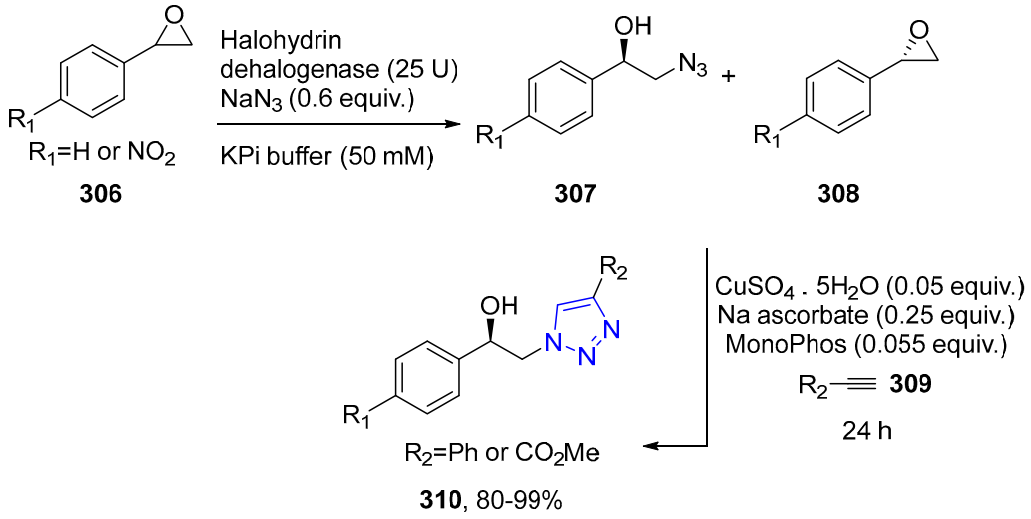
Proulx and Lubell described the synthesis of aza-1,2,3-triazole-3-alaninyl **305** in a copper-catalyzed tandem aryl azide formation/1,3-dipolar cycloaddition approach. For that, a 1,3-dipolar cycloaddition with aryl iodides, sodium azide, and copper iodide must be carried out in a tandem aryl azide formation/cycloaddition reaction cascade (Scheme 95) [119].



Scheme 95. Proulx and Lubell (2010).

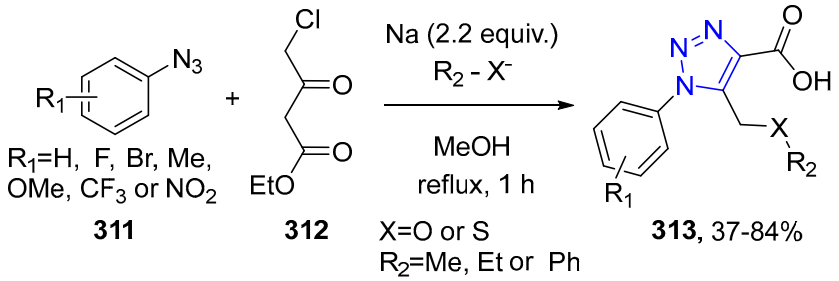
Campbell-Verduyn et al. attained the combination of the azide-induced ring opening of epoxides **306** with the copper-catalyzed 1,3-dipolar cycloaddition of azides **307** and alkynes **309**. The reaction

protocol was carried out by the one-pot tandem biocatalytic enantioselective epoxide ring opening and click reaction to obtain hydroxy triazoles **310** in aqueous solution with neutral pH at room temperature (Scheme 96) [120].



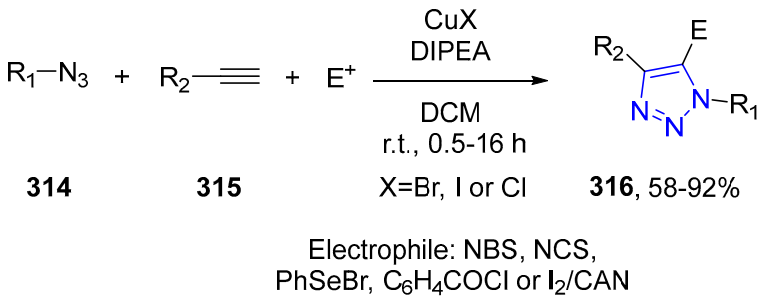
Scheme 96. Campbell-Verduyn et al. (2010).

The team of Pokhodylo reported the synthesis of 1-(*R*-phenyl)-5-(*R*-methyl)-1*H*-1,2,3-triazole-4-carboxylic acids **313**. Various substituted 1,2,3-triazole acids were obtained in good yields by a three-component reaction involving arylazides **311**, ethyl 4-chloro-3-oxobutanoate **312**, and either O- or S-nucleophiles in the presence of a base. The reaction most probably proceeded as a [3+2] cyclocondensation reaction between arylazide and ethyl 4-chloro-3-oxobutanoate followed by an additional nucleophilic substitution of chlorine in the chloromethyl group (Scheme 97) [121].



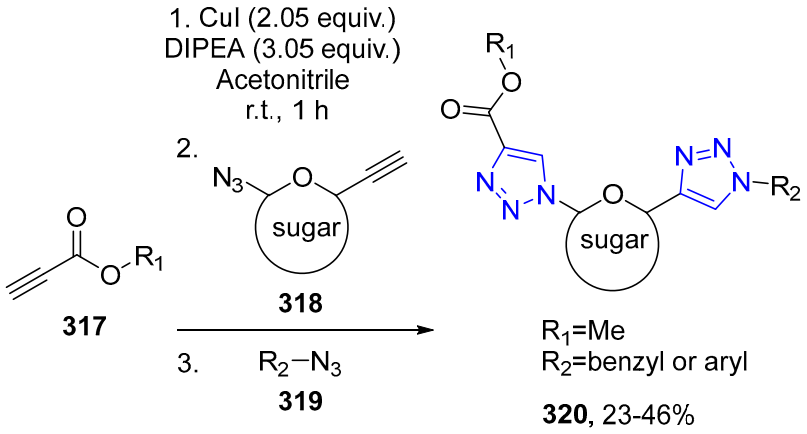
Scheme 97. Pokhodylo et al. (2010).

Malnuit and co-workers also published a three-component approach to synthesize 4,5-functionalized triazolyl-nucleosides **316**. Their method involved the one-pot azide–alkyne 1,3-cycloaddition/electrophilic addition tandem reaction (Scheme 98) [122].



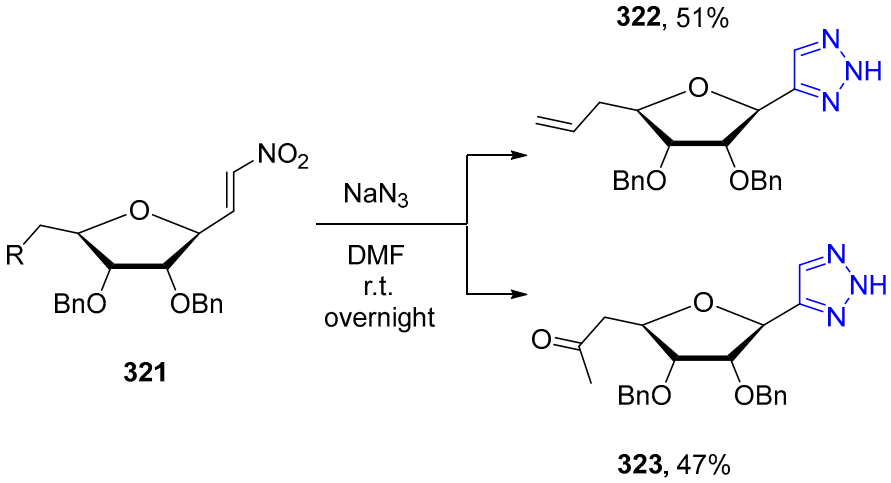
Scheme 98. Malnuit et al. (2009).

The group of Kaliappan studied click chemistry on sugar-derived alkynes **318**. The methodology presented showed a tandem 'click–click' approach to the synthesis of 1,4-disubstituted 1,2,3-bistriazoles **320** from sugar-derived alkynes in moderate yields (Scheme 99) [123].



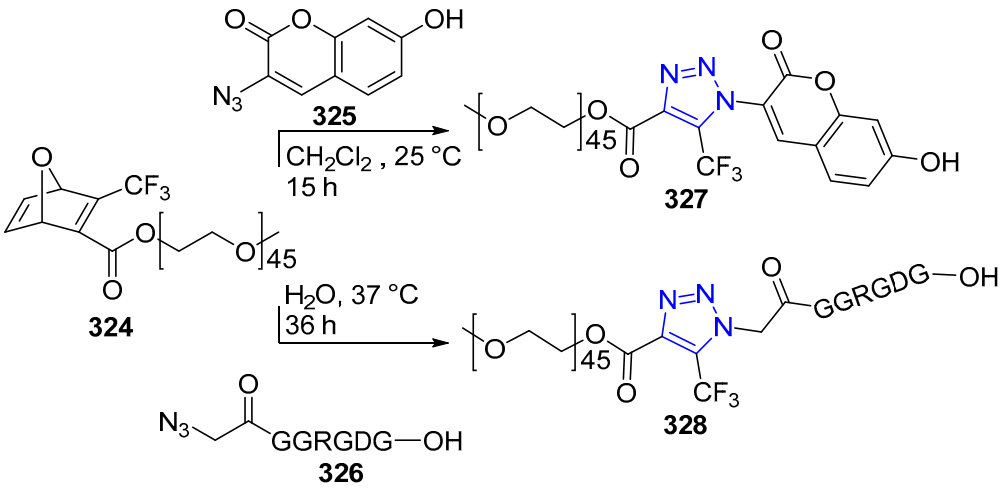
Scheme 99. Kaliappan et al. (2009).

Zou et al. achieved 1,5-disubstituted triazole-fused sugars **322**, **323** by applying a tandem 1,3-dipolar cycloaddition and intramolecular Michael addition approach. The team prepared triazole-fused carbohydrates by treating nitroalkene-containing C-glycosides **321** with sodium azide (Scheme 100) [124].



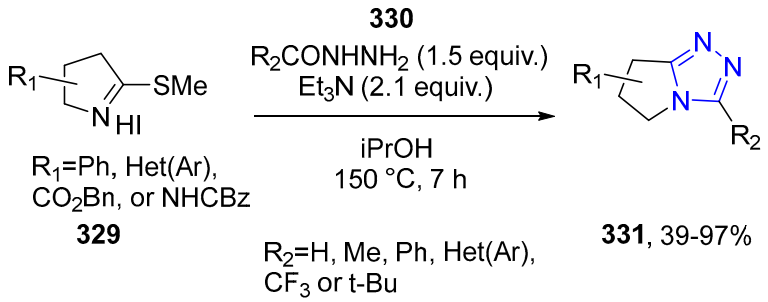
Scheme 100. Zou et al. (2009).

Van Berkel et al. prepared the stable 1,2,3-triazole-linked compounds **327, 328** using a tandem [3+2] cycloaddition–retro-Diels–Alder ligation method. The library was obtained from trifluoromethyl-substituted oxanorbornadiene **324** and azides **325**, **326** (Scheme 101) [125].



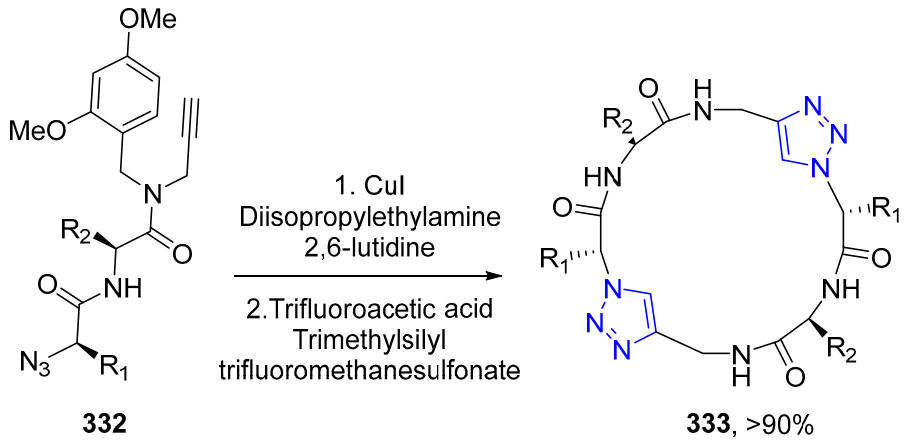
Scheme 101. Van Berkel et al. (2007).

Marco and Kuduk performed the synthesis of fused [5,5]-1,2,4-triazoles **331** with a tandem cyclopropane rearrangement–cyclization sequence. Optimization of the cyclization of the amidrazone **330** was achieved thermally using isopropanol (iPrOH) with trimethylamine (Et_3N). The strategy was applied to the synthesisof 3-substituted-7-aryl-pyrrolo-1,2,4-triazoles (Scheme 102) [126].



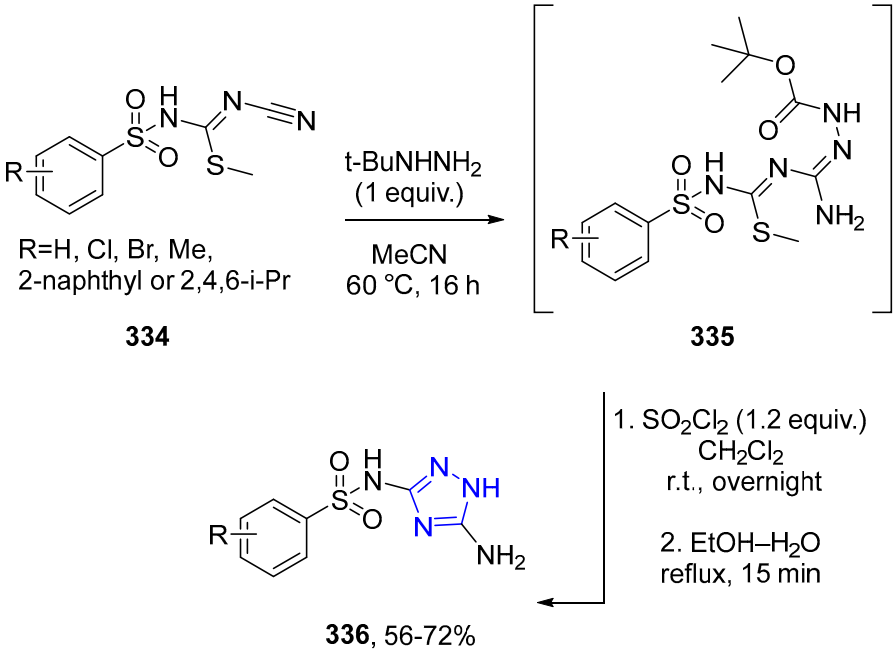
Scheme 102. Marco and Kuduk (2006).

The group of van Maarseveen reported a tandem dimerization−macrocyclization approach. To achieve this, they used 1,3-dipolar azide−alkyne cycloaddition reactions in solution phase syntheses of C2 symmetric cyclic peptide scaffolds bearing triazole E2-amino acids **333** as dipeptide surrogates (Scheme 103) [127].



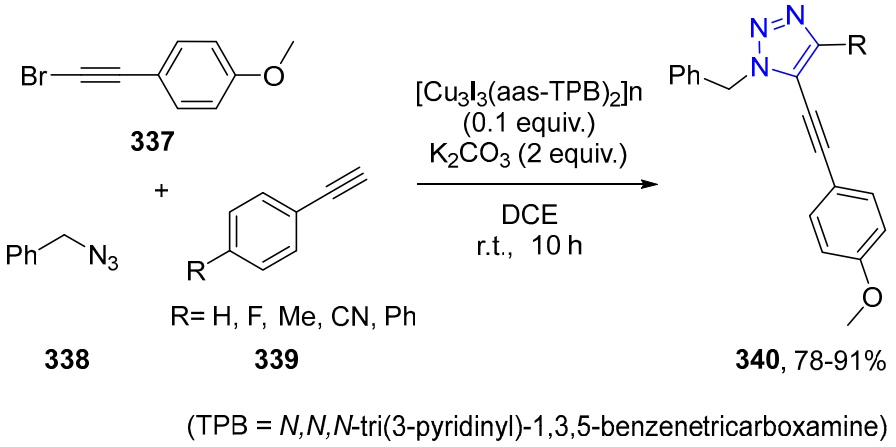
Scheme 103. Van Maarseveen et al. (2005).

Chibale and co-workers synthesized arenesulfonamide derivatives of 3,5-diamino-1,2,4-triazole **336**. The formation of the triazole ring on a large scale, in pure form and high yield, was obtained by tandem reaction promoted by sulfuryl chloride. The expected compounds were synthesized without the use of the highly hazardous hydrazine (Scheme 104) [128].



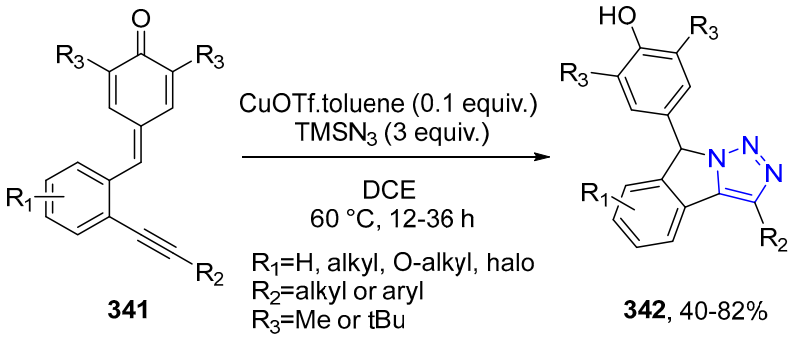
Scheme 104. Chibale et al. (2002).

The team of Guo optimized a three-component tandem click/alkynylation reaction using an efficient catalyst complex prepared previously by them. The desired triazoles **340** were obtained from bromoalkyne **337**, benzyl azide **338,** and terminal alkynes **339** (Scheme 105) [129].



Scheme 105. Guo et al. (2018).

Jadhav and co-workers developed an approach to obtain 1,2,3-triazole-fused isoindolines **342**. This methodology applied a Cu(I)-catalyzed 1,6-conjugate addition of azides to *o*-alkynylated *p*-quinone methides and then an intramolecular click cycloaddition (Scheme 106) [130].



Scheme 106. Jadhav et al. (2018).

Final note on Triazole: In all the studies that described the synthesis of the triazole ring using a tandem-catalyzed reaction, Cu, Pd, Ag, or Ru was used. More than 90% of the cases reported the use of copper.

4.2.6. Isoxazole

The isoxazole ring is an important pharmacophore in modern drug discovery. This nitrogen heterocyclic compound presents a wide variety of medicinal and biological activities (Figure 10) [2,22].

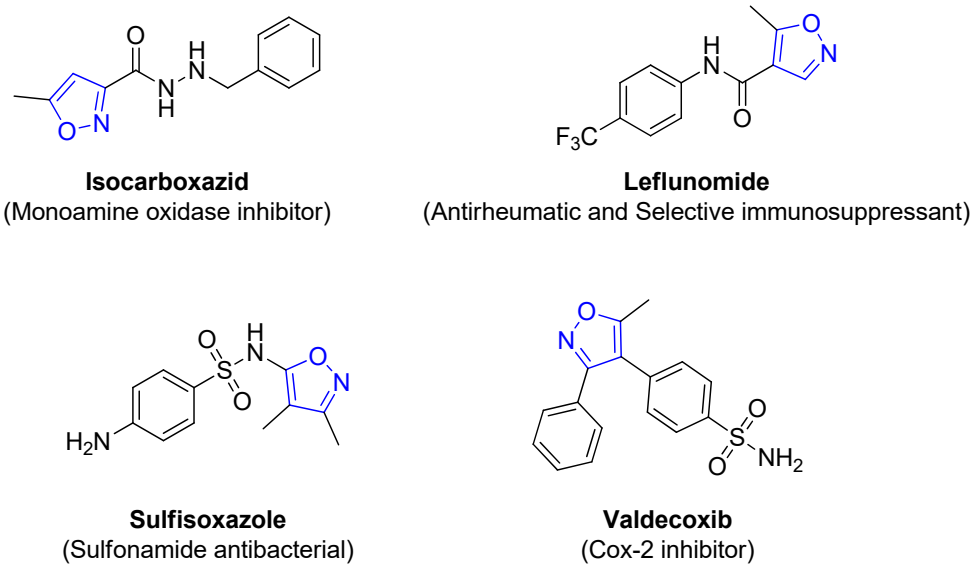
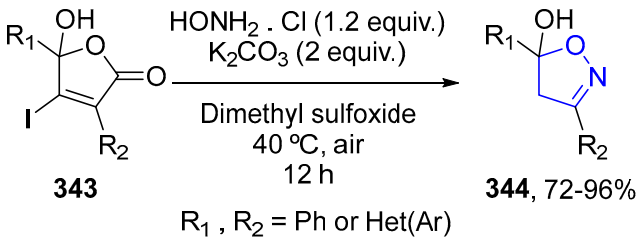


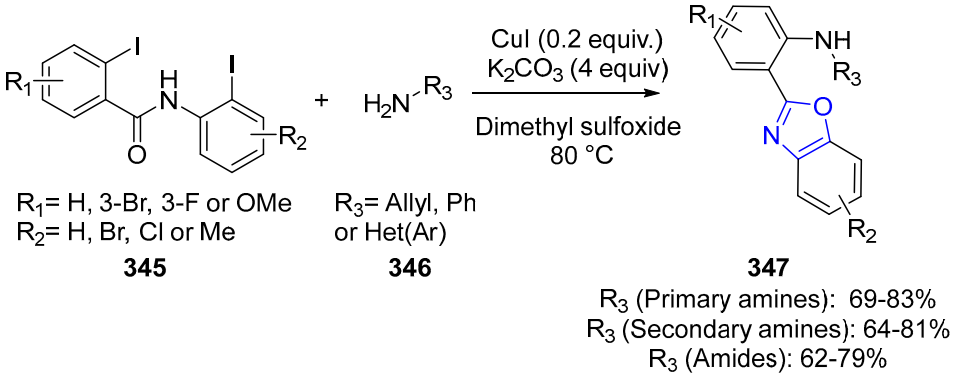
Figure 10. Drugs containing the isoxazole ring.

Li et al. developed a procedure to obtain 5-hydroxy-4,5-dihydroisoxazoles **344** via a tandem reaction including ring-opening, Michael addition, and ring-closure. This metal-free approach afforded several 5-hydroxy-4,5-dihydroisoxazoles in excellent yields from 4-iodo-5-hydroxy-furan-2-ones **343** and hydroxylamine hydrochloride (Scheme 107) [131].



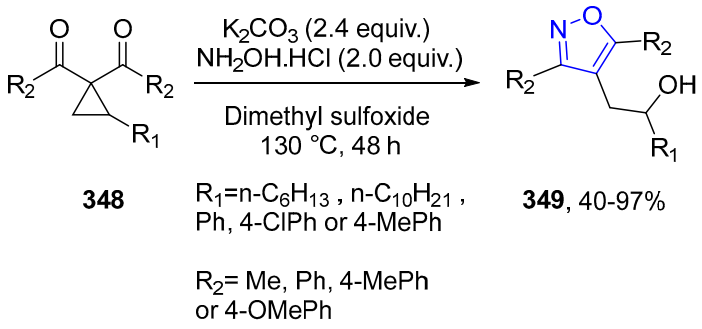
Scheme 107. Li et al. (2019).

Kavala and co-workers described the reaction of 2-(2-halophenyl)halobenzamides **345** with nitrogen nucleophiles **346** for the preparation of benzoxazole derivatives **347**. This procedure involved copper-catalyzed one-pot tandem C–N/C–O coupling reactions (Scheme 108) [132].



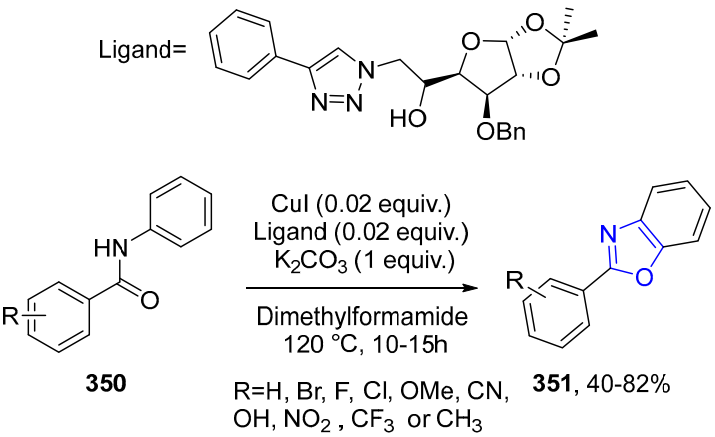
Scheme 108. Kavala et al. (2012).

Wei and co-workers reported a one-pot tandem Cloke–Wilson/Boulton–Katritzky reaction of cyclopropylketones **348** with a hydroxylamine. In this study, the hydroxylamine was recycled internally and served as both a catalyst and a reactant. (Scheme 109) [133].



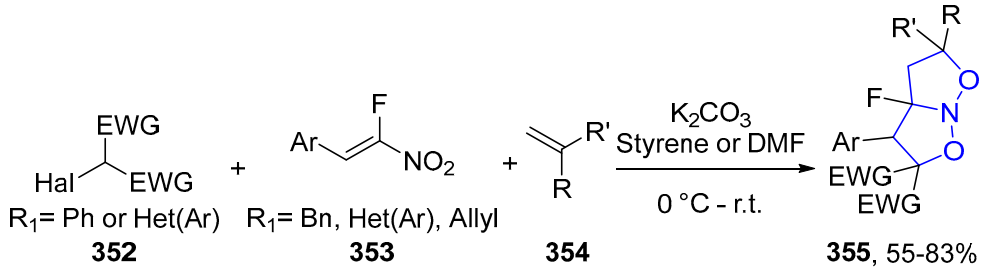
Scheme 109. Wei et al. (2018).

Mishra and co-workers successfully developed a route to prepare 2-aryl benzoxazoles **351** using triazolyl derivatives of D-glucose as potential ligands for Cu(I)-catalyzed cross-coupling (Scheme 110). The approach involved an intramolecular Ullmann-type C-heteroatom coupling. Additionally, it was applied for the synthesis of other heterocycles (2-arylbenzothiazoles, 2-arylbenzimidazoles, 2-aminobenzothiazoles, and benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones) [134].



Scheme 110. Mishra et al. (2019).

Motornov et al. developed a tandem [4+1]/[3+2] cycloaddition from various fluoronitroalkenes, halogenated dicarbonyl compounds, and dipolarophiles. The group proposed a mechanism that included the intermediate formation of elusive 3-fluoro-isoxazoline-*N*-oxides as a key point in the preparation of the desired products **355** (Scheme 111) [135].



Scheme 111. Motornov et al. (2018).

Final note on Isoxazole: The teams that have demonstrated isoxazole ring synthesis using a tandem-catalyzed approach used CuI as a complex.

5. Conclusions

As showcased by the examples in this review, tandem catalysis can be a valid tool for medicinal chemists because of the high atom economy generated. Tandem reactions have often been used particularly in the total synthesis sequences of natural products, and we have seen its applicability to interesting heterocyclic substrates. Tandem reactions, in which several catalysts and reagents are combined in a single reaction flask with a sequence of catalytic steps, are attractive from the point of view of reducing waste and time. These reactions can be carried out by radical and pericyclic cascades or by nucleophilic and electrophilic attack, but when this type of reaction is combined with transition-metal-catalytic processes, we increase the power of the sequences in terms of atom economy, and reduction of reaction time and waste. Being able to carry out this type of sequence in so-called green solvents would, of course, be an additional step toward limiting the environmental impact of the development of interesting molecules.

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